CHEMICAL HERITAGE FOUNDATION

GERALD WEISSMANN

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Arthur Daemmrich

at

The Marine Biological Laboratory
Woods Hole, Massachusetts

on

2 August 2007

(With Subsequent Corrections and Additions)

Gerald Weissmann

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GERALD WEISSMANN

1930 Born in Vienna, Austria on 7 August

Education

1950 B.A., Fine Arts, Columbia College
1954 M.D., New York University

Clinical Training

Mt. Sinai Hospital of New York
1954-1955 Intern
1957-1958 Assistant Resident in Medicine

Bellevue Hospital, New York
1959-1960 Chief Resident in Medicine

Research Appointments

New York University
1958-1959 Fellow, Arthritis and Rheumatism Foundation, Departments of Biochemistry and Medicine (Mentor: Severo Ochoa)
1959-1960 Research Assistant, Department of Medicine

Strangeways Research Laboratory, University of Cambridge, Cambridge, England
1960-1961 USPHS Special Research Fellow, Department of Biophysics (Mentor Dame Honor Fell)

Professional Experience

New York University School of Medicine
1959-1961 Instructor in Medicine
1962-1965 Assistant Professor of Medicine
1966-1970 Associate Professor of Medicine
1970-present Professor of Medicine
1970-1973 Director, Division of Cell Biology
1973-2000 Director, Division of Rheumatology

2000-present	Director of Biotechnology Study Center
2003-present	Research Professor of Medicine
2003-present	Professor of Medicine Emeritus

Pharmaceutical and Biotechnology

1973-1976	Scientific Advisory Board, Ethicon Company, New Brunswick, New Jersey
1982-1986	Scientific Advisory Board, BioResponse, Menlo Park, California
1972-present	Consultant, Inflammation and Arthritis (ad hoc) Pfizer, Searle, Riker, Upjohn
1982-2000	Director, Co-Founder (with E. C. Whitehead) and Chair, Scientific Advisory Board, The Liposome Company, Princeton, New Jersey

Editorial

1975-2001	Editor in Chief, *Inflammation*
1979-1989	Editor-in Chief, *Advances in Inflammation Research*
1989-1994	Editor in Chief, *MD Magazine*
2005-present	Editor in Chief, *The FASEB Journal*

Honors

1966	Author of "Citation Classic" (Lysosomes and Joint Disease)
1974	Author of "Citation Classic" (Cyclic Nucleotides and Neutrophils)
1972	Allesandro Robecchi International Prize for Rheumatology, Aix-lex-Bains
1973-1974	Guggenheim Fellow
1978	University of Bologna Nine-Hundreth Anniversary Medal (with Lewis Thomas and others)
1980	Gruber Award for Cancer Research (with Emil Frei, III)
1980	Solomon A. Berson Medical Alumni Achievement Award in Clinical Sciences
1981	Bunim Lecturer and Medalist, American Rheumatism Association
1982	Fellow, American Association for the Advancement of Science
1987	National Institutes of Health Merit Award
1987	Rockefeller Foundation Residency at Bellagio
1988	Marine Biological Laboratory Centennial Award for Leadership in Biomedical Sciences (with DeWitt Stetten and James Wyngaarden)
1990	Hiram Maxim Award for Scientific Communication
1992	Distinguished Investigator Award, American College of Rheumatology
1993	Charles Plotz Award, Arthritis Foundation of New York
1997	Paul Klemperer Medal, New York Academy of Medicine
1998	Rockefeller Foundation Residency at Bellagio
2001	Paul Klemperer Award & Lecture, American College of Rheumatology

2001	“Research Hero” Award, Arthritis foundation Fiftieth Anniversary
2002	Academia Nazionale die Lincei
2005	Presidential Gold Medal, American College of Rheumatology
2007	Chairman, Prix Galien USA

ABSTRACT

Gerald Weissmann's oral history begins with a discussion of his family and childhood in Vienna, Austria. While still very young, Weissmann and his family fled the Nazi *Anschluss*. After their journey from Vienna to Italy, Paris, and London, and before finally reaching New York, Weissmann developed a political awareness at a young age. Throughout his youth in New York City, Weissmann's father, also a rheumatologist, exerted a positive influence on Gerald's own career path. Additionally, Weissmann was influenced and mentored by his father's friend and colleague, the famed pathologist, Paul D. Klemperer. After earning a bachelor's degree in fine arts from Columbia College, Weissmann, entered medical school at New York University [NYU], citing his love of science as a primary reason for following such a career path. Following an internship year at Mount Sinai Hospital, Weissmann entered the army and, while stationed at Fort Dix Army Hospital in New Jersey, he published his first scientific paper. Following his time in the army, Weissmann faced a decision between following a purely clinical career in rheumatology, like his father, or an academic one, focused on medicine and rheumatology research. Having opted for the research career, Weissmann continued his residency program at Mount Sinai Hospital and became chief resident at Bellevue Hospital under Lewis Thomas. Concurrent with his residency, Weissmann undertook research at NYU with Severo Ochoa. After becoming an Instructor in Medicine at NYU, Weissmann traveled to the Strangeways Research Laboratory at the University of Cambridge to collaborate with Dame Honor Fell studying the effects of excess Vitamin A on bone rudiment and cartilage. At approximately the same time, Weissmann's research transitioned from studying lysosomes into studying lipids. In the mid-1960s, Weissmann, along with close friend, Alec D. Bangham, discovered liposomes and developed a new field of research. In 1982 Weissmann and E.C. [Jack] Whitehead founded The Liposome Company, which received FDA approval for the drugs Abelcet and Myocet. In this oral history, Weissmann also discusses, in great detail, the origins of the Pew Biomedical Scholars Program. Although he heaped most praise on Joshua Lederberg for the program, Weissmann also described his influence and that of other early Advisory Board members. Contrasting the Pew funding for biomedical scientists with larger funding bodies like the NIH, Weissmann extolled the benefits of funding creative young scientists. In conclusion, Weissmann discusses his own popular scientific writings and larger issues in the history and sociology of science.

INTERVIEWER

Arthur Daemmrich is an assistant professor in Business, Government, and International Economy at Harvard Business School (HBS) and a Senior Research Fellow at the Chemical Heritage Foundation. His research and teaching focus on business in regulated environments and international comparative analysis of risk and regulation. At HBS he also plays an active role in an interdisciplinary Healthcare Initiative, advancing scholarship and developing applied lessons for the business of creating and delivering health services and health-related technologies. Daemmrich was previously the director of the Center for Contemporary History and Policy at the Chemical Heritage Foundation. He earned a Ph.D. in

Science and Technology Studies from Cornell University in 2002 and has held fellowships at the Social Science Research Council/Berlin Program for Advanced German and European Studies, the Kennedy School of Government at Harvard University, and the Chemical Heritage Foundation. He has published widely on pharmaceutical and chemical regulation, biotechnology business and policy, innovation, and the history of science.

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INTERVIEWER: **Arthur Daemmrich**

LOCATION: **The Marine Biological Laboratory**
Woods Hole, Massachusetts

DATE: **2 August 2007**

DAEMMRICH: Gerry, if we could begin, why don't you tell us a little about your parents and early childhood?

WEISSMANN: Well, I was raised in a middle to upper-middle class family in Vienna, Austria. My father was a rheumatologist and he had an appointment at one of the university clinics. It was the usual middle-European background until [Adolf] Hitler came to power. After various stops in Italy, where we were waiting for a visa to get to the United States, we arrived in England. It is not an amusing story; Hitler came in March and we left in June.

DAEMMRICH: This is the *Anschluss* [the annexation of Austria into Greater Germany by the Nazi regime], correct?

WEISSMANN: In 1938, I was seven years old and in the second grade. About a month after the *Anschluss*, Austrian police with swastika armbands came and took me and the other Jewish kid in the class and dragged us out of school in the middle of the day. They took us to a different school that was made entirely for Jews. It was in the other part of town. As we left, there was a lot of jeering from our classmates and even their parents because they were watching during their lunch hour. Before we left, they made us scrub the schoolyard with brushes—a memorable experience.

I went there for school for awhile and I still have the records, believe it or not. The Nazis in Vienna hadn't quite gotten everything tagged yet. They didn't have the yellow stars for us to wear and they didn't have *Juden* stamped on passports yet. My mother simply signed up for a day trip to Florence[, Italy], which you could still do, through Thomas Cook Tours. Travel restrictions hadn't gotten tight yet. And we left with nothing and stayed in Naples where it was cheap. And I don't know how much money my parents had with them.

DAEMMRICH: The whole family went together as one group?

WEISSMANN: My mother, my father, and me. That's all there was. Obviously, being young, I thought we were going to Italy for vacation. We had distant relatives in the United States. Amazingly enough, one of them was a police captain in New York named Lustbader, a distant cousin of my mother. He wrote to [New York] Senator [Robert] Wagner. Senator Wagner then urged the American Consul in Naples[, Italy] to place our names on the quota that would allow our admission to the United States. I still have the letter written by Senator Wagner and, consequently, I've always voted Democratic. My views on immigration are those of liberal democrats.

My father's work in rheumatology also helped us in our travels to the United States. While still in Vienna, my dad had just enough money to purchase tickets for transport from England to the United States, which you could still do at the time. They were open tickets, first class, to come on the American Line from [England] to New York for the three of us. So he had the tickets, but we had no way of getting to Liverpool from Paris[, France]. My parents were pretty broke and I remember, quite distinctly, the train ride from Italy and our stop in Paris. We stayed at some cheap hotel. On a rainy day, I had to stand under the awning of Fouquet's, one of the cafes on the Champs-Elysees, while my father went to visit the editor of the *Revue du Rhumatisme*.[1] He just published an article on rheumatology injections in joints and he wanted to see if he could borrow some money from the editor. I do wonder if I would ever do that now for someone whose work I just published. I might. I don't know. But it was generous. He gave my father enough money to get us all to London[, England] where my aunt Helen had been for a number of years.

Representatives of the Woburn House, which is a settlement house based on the Toynbee Hall model, received us in London. Originally, the East End of London and the settlement houses were designed to accommodate Polish Jews, Irish refugees, et cetera. I remember being given a tweed jacket by the representatives because that was the norm for dress. [laughter]

I went to school for a couple of months in England and then we came to the United States. My father, within a year and a half, got his license to practice medicine. He had an office on 86th Street between Riverside Drive and West End Avenue for many years. Many of his patients were also Viennese refugees and many of his colleagues were there. There was a whole Viennese émigré colony including good scientists like Paul [D.] Klemperer and Otto Loewi, whom my father knew well and whom I had the opportunity to meet. Klemperer was a pathologist at Mount Sinai [Hospital] at the time and that's where I first got to know him. My interest in rheumatology must have begun when I was in college—we'll get to that in a minute—when he took me to a meeting, in 1950 I believe, when Phillip [S.] Hench showed movies of people miraculously walking after they had been given cortisone.

DAEMMRICH: I actually wanted to come to that episode a little later.

WEISSMANN: That got me interested in rheumatology as something you could work with and be excited about. I had been a pretty good painter and I'd been going to art school since I was eleven. While attending college, in 1949 I believe, I had my first one-man show—including a great portrait of Mark Van Doren. It was reviewed in most of the papers. That helped me decide that I would resolve my Oedipal complex and identify with my father. [laughter]

DAEMMRICH: Let me take you back a little bit. Are there other memories of Vienna from when you were really young?

WEISSMANN: Very little. I just remember playgrounds, parks, friends. My maternal grandfather owned a couple of well-known coffee houses described by Joseph Wechsberg in a book called *Looking for a Bluebird*.[2] He was a café owner. But I remember very little about my childhood in Vienna: school friends and playgrounds. I went back to visit a number of years later for the first and last time—consciously the last time. And it was an experience I won't discuss. I'm not at all like Eric Kandel: unlike Eric, I have not resolved my fury at the Austrians (as opposed to the Germans).

DAEMMRICH: Fair enough. My own family is originally from Germany and I know my father has been back only very rarely.

WEISSMANN: I think Germany has handled it better, but I'm sure some Germans truly haven't. Look at Günter Grass, who was enchanted by the Nazis as a youth. He was older than I was. But even then I knew what was going on. I remember distinctly when we were in Naples, the cheapest place you could live in was Ischia. It cost almost nothing to stay there—it was dogville. I distinctly remember listening to the radio when the Spanish Republic fell and I knew my parents were completely depressed, especially since they'd driven through the city of Naples and seen the Italian Fascists rejoice. And so you know what politics are at that age. Grass was older than I was when he joined the Waffen-SS. Fuck him. That will be recorded I hope.

I actually ran into Günter Grass. During the Nobel Centenary in 2001, I was a guest of my good friend Bengt Samuelsson. [V. S.] Naipaul had just given the literature speech and John Vane stayed upstairs to chat with him because they're both English. I was going down the stairs with Bengt Samuelsson and realized that we'd forgotten to tell John Vane which restaurant we're going to. I rushed up the stairs and I ran over a gnarled dwarf, who fell down. I looked at him and said, "Entschuldigen [Pardon me], Herr Grass." So when somebody asks, "did you run into Günter Grass," I can say that I literally ran into Günter Grass.

DAEMMRICH: You knocked him over.

WEISSMANN: I'm the man that ran into Günter Grass. Had I known then what I know now, I wouldn't have helped him up. [laughter]

DAEMMRICH: Your father was a practicing rheumatologist?

WEISSMANN: Yes, absolutely.

DAEMMRICH: Do you remember if he talked about patients when he was at home during your childhood? Did he talk about the challenges related to how he was treating people at the time?

WEISSMANN: Yes. Certainly not early on, but once I was in high school I began to understand what he was doing. In fact, I remember when I was in my first year of medical school I illustrated one of his articles, showing how to inject a hip joint. It was my first publication in a medical journal.[3]

DAEMMRICH: What were they injecting into joints at the time?

WEISSMANN: Salt solutions that yielded active anions. Hyaluronate is a viscous material, which turns fluid if de-polymerized. Physicians were injecting these salt solutions based on the assumption that this would loosen the fluid within the joint. The polymer chemistry of that was thought very simple. You raise anions and the anions on hyaluronate discharge, so the polymer lengthens and that makes it easier for the fluid to move in the joint. Currently, people inject hyaluronate that is itself not too viscous. Essentially, it was a way of doing what we now do by other means.

DAEMMRICH: Interesting.

WEISSMANN: In fact my father published an article about this at the time. He published a lot; I'd say a dozen or two papers.

DAEMMRICH: Were those mostly patient observational studies?

WEISSMANN: Yes, but also case reports. For example, people thought that rheumatic fever was caused by tuberculosis in some way. He published a case study showing that it didn't work that way and that there was no relationship between them, but that there was a relationship between rheumatic fever and other sorts of infection. He did what smart, practicing physicians did in those days: he described patients and what was done for those patients. At a university clinic you had all the records about what was done to a patient.

DAEMMRICH: Now, you went to Columbia University for your undergraduate degree.

WEISSMANN: Columbia College, which is a liberal arts college and the smallest of the Ivy League schools—only about two and half thousand people in it. It was the golden age of liberal arts. My teachers—and not just people on campus, but also the people who taught me in small groups—were Mark Van Doren, Joseph Wood Krutch, Lionel Trilling, and Jacques Barzun. The man who really taught me how to write and turned me on was Mark Van Doren. I was one of the editors of *The Columbia Review* as well as the art editor and cartoonist for the *Jester*.

My most fateful accident happened trying out for freshman football. I clipped my knee and my meniscus tore. I was brought to the Hospital for Joint Diseases, which in those days was up where North Harlem Hospital is now. My dad said, "Do not operate. Put it in a cast. If you operate, you've got osteoarthritis when you're older. Don't operate. Put it in a cast. It'll heal by itself and reform the cartilage." And I've been running and playing tennis ever since with no problem.

However, the accident had another fortuitous fallout. The accident occurred in the spring of my freshman year and I had been trying out for the next season of football. I had a 'cast' party at my parents' house on 86th street with all of my friends and one of them brought along a beautiful high school senior named Ann Raphael, who I met for the first time then. The next year I met her again when she was at Vassar College, though I was there for somebody else. That's been it ever since. The accident happened and that's how I met my wife, and that's been it forever.

DAEMMRICH: That's a wonderful cascade of coincidences. At what point did you pick a major in college?

WEISSMANN: Well, I majored in fine arts. I arrived as an undergraduate at Columbia in 1947 and you could pick a couple of things. I wanted to take a course in fine arts for undergraduates, but it seemed silly because I knew all that stuff and I'd been studying art since day one. I didn't have to be told who Vincent Van Gogh or Nicolas Poussin were. Poussin was my favorite painter. I went to see the chairman of the department, Meyer Schapiro, a well-known art historian. I said, "Sir, can I take your grad course," which focused on impressionism and modern art—Schapiro's specialty. He said, "Sure." He talked to me for awhile and then he

said, "Would you write me a paper?" He looked around his room and he handed me a copy of *Les Demoiselles d'Avignon* by Pablo Picasso.[4] I looked at it as a piece of cake.

DAEMMRICH: Really?

WEISSMANN: Yes, I knew the picture rather well. It progresses over there, begins with African art, goes to analytical then synthetic cubism. I mean this is like asking me right now, tell me about a liposome. And so I gave him the paper and next he said, "Okay, take the course and you can help me, help my graduate assistants in grading papers."

DAEMMRICH: You were promoted to a graduate-level assistant in your freshman year.

WEISSMANN: Well, and again, it was because I'd been doing art in high school.

DAEMMRICH: Did you take courses in creative writing or in science writing? How did that interest develop?

WEISSMANN: I started writing from when I was very young. My future was written out for me. I was editor of the *Journal of Biology* at the Bronx High School of Science and when I graduated, I received the prize for English and art. I mean, I hate to be self serving—

DAEMMRICH: Were there particular high school teachers who mentored you on this path?

WEISSMANN: Yes, there was one teacher who taught art at Bronx Science. There was Toby Kurzband—a fine man. Right during and after the war people had a hard time getting counselors at camp and he picked me to be a counselor at this camp at Bantam Lake, Connecticut.

DAEMMRICH: Just one or two other questions about this early phase of your life, as it were. How did you find the experience of learning English? Had your parents spoken any English at home?

WEISSMANN: They did not know one word of English. When I was younger, just for a year or two before we left, I had an American governess. So I did speak a few words of English. I guess nowadays you call it an *au pair*, but in those days you called it a governess.

DAEMMRICH: In the community you moved into in New York, there were a lot of expatriates from Vienna.

WEISSMANN: Not many, no. That was my father's patient group. When I was in England, I was sent to school immediately, just cold turkey. You learn. By the time I got on the boat two months later, I was an eight-year-old kid. The cutoff, if you notice: if you come here before twelve, you don't have an accent. If you come here after twelve, you do.

You can tell that [Henry] Kissinger came as a late teenager. But it's like a tan. [laughter] It fades if you haven't been out in a long time. I play tennis with an accent because I didn't really start playing tennis until about nineteen or twenty. Those people who played from the beginning play tennis without an accent. You don't quite have the same moves or ease in movement and you can tell immediately who's been trained and who hasn't.

DAEMMRICH: At Columbia you must also have taken some science courses?

WEISSMANN: Yes, originally I took them simply to satisfy my dad. He said, "You're going to be a doctor." I fell in love with the arts and was relatively uninterested in science. In fact, I got a C+ in organic chemistry. I also broke a lot of glassware. The man who gave me the C+ was named [Charles R.] Dawson, who was a very fine chemist and was one of R[obert] B[urns] Woodward's students. I thought he was brilliant, but he thought I did terribly. I loved him. He was delighted after I'd worked on liposomes and he asked me to talk to the American Chemical Society [ACS] on liposome structure. I did not remind him about the C+.

DAEMMRICH: But he was there?

WEISSMANN: Yes. Yes. It was nice. Now there's another part of my family that's crystallographers. My father's brother, Sigmund, who was in the National Academy of Engineering. He came to the United States about two years after we did and got his Ph.D. at Brooklyn Polytechnic Institute. He was a professor of material science at Rutgers [State University of New Jersey], and also a great concert pianist, but he was a crystallographer. My cousin, Lisa [Heller-Kallai], who's my age, is now at the Hebrew University of Jerusalem—she works there and is also a crystallographer.

So that's the other part of my family and Sigi [Sigmund] was a very major influence in my life. He was a pure scientist from the beginning and discovered crystal structures by a double-beam diffraction technique, which we use to measure strain dislocation in metals. We published the structure of hydroxyapatite. In the ASTM [American Society for Testing and

Materials] manual, hydroxyapatite is associated with Weissmann and Weissmann: that's Sigi and myself, which I did when I was actually a resident.[5] But that was all. It was another kind of influence as well. Despite the fact I didn't get very excited about science in college, it was pretty routine. I got excited about arts and writing and dating and so forth.

DAEMMRICH: Family gatherings must have been pretty exciting with thought provoking scientific discussions.

WEISSMANN: Well, he was brought up in the Gymnasium tradition and had—

DAEMMRICH: Studied Greek and Latin.

WEISSMANN: Yes. Also he was a fine classical pianist and my father's a violinist; it was just classic, central-European stuff. Consequently, I never thought of the arts and the sciences to be particularly antagonistic. You just did both.

DAEMMRICH: You married, then, just when you received your undergraduate degree?

WEISSMANN: Well, no. We were dating for years, but in my day you didn't get married until you could support your wife or she could support you. By my third year of medical school, Ann was working at the Metropolitan Museum of Art. She just had graduated from Vassar College and went to work for a man named Emmanuel Winternitz, the curator of musical instruments at the museum. She had a salary. With the help of her parents, my parents, and her salary, we were able to get married.

DAEMMRICH: Did you go to medical school directly with the B.A. from Columbia in 1950?

WEISSMANN: Yes, I then went to the New York University [NYU] School of Medicine; I did not get into Columbia University College of Physicians and Surgeons. They had a very strict quota with no more than about 10 percent Jews at the time and my science grades weren't spectacular. Or maybe 15 percent. Ivy League schools in general had those quotas and medical schools were the tightest. I've used in print that well known clerihew about the Ivy League colleges which went, "Harvard [University]'s run by gentlemen and Yale [University] is run by booze; Princeton [University]'s for the southerners, Columbia for the Jews." [jingle]

DAEMMRICH: I have never heard that one. I guess Penn [University of Pennsylvania] didn't even make the list, which is where I went to undergrad. I know that during that time period a lot of chemical and pharmaceutical companies recruited only white gentiles.

WEISSMANN: Oh, yes.

DAEMMRICH: It's astonishing to reflect on because people like to think of the United States as a safe haven during and after World War II.

WEISSMANN: Oh, no. I think it's in *The Year of the Genome*[*: A Diary of the Biological Revolution*]—I forget where I publish things—but I had a whole piece on that.[6] Actually, it had to do with the whole Lewis Thomas tradition. I was the first known Jewish chief resident at Bellevue Hospital, believe it or not. The student body in those days was 60 to 75 percent Jewish and yet the Bellevue house staff was run by old Rockefeller [University] people like William S. Tillett. They were very overtly or covertly…I wouldn't say anti-Semitic, but I would say Jewish exclusionary. There was one before me named Arthur Fox, but they didn't know he was Jewish. But when Lewis Thomas came to NYU [New York University], that just changed completely.

DAEMMRICH: Was the prevailing sense at the time that young Jewish boys became M.D.s and then just practiced medicine as opposed to entering the research track?

WEISSMANN: Yes, in fact I'll give you a perfect example. I interned at Mount Sinai Hospital because my father was there, but also I just wanted to stay in New York. I'm a New Yorker. I wouldn't leave it for anything. I couldn't apply to Cornell's New York Hospital for an internship or residency because there were no known Jews working there at that time. Columbia took a few, but not too many. It was the end of the Korean War. I wasn't sure whether I wanted to pursue more clinical medicine. I really got interested in science, in medical science. I remember distinctly chatting with my wife and parents about what to do. I'm trying to remember the exact conversation with Paul Klemperer, the pathologist at Mount Sinai who coined the expression "Connective Tissue Disease." He told me, "You won't get a job in academia. You're going to have a hard time. Look at me, I couldn't get a professorship at a university." Perhaps that's why I'm sort of proud that I've gotten two Klemperer awards for connective tissue research.

I decided to take a moratorium and I joined the army. There were many reasons, but I also had major patriotic motives at the time. I thought I owed the country something and so I joined the army. In the army, at Fort Dix Army Hospital, I wrote my first scientific paper, where I described Sjogren's Syndrome for the first time in the United States. I found that it was associated with positive rheumatoid factor.[7] That was early, early on.

Then I came back to Mount Sinai to finish my residency. By that time, 1958, my father had died of a coronary on a cold winter night while making a house call. I was presented with a choice: should I follow my father and take over his practice, which was doing well, or go on to something new. By that time I'd decided to do academic medicine and to do research. I got excited by connective tissue, arthritis, inflammation, and so on. I remember having long talks with my wife and I said, "Let's go for it."

DAEMMRICH: The famous cortisone year when Hench published his study is 1950 or 1951, right when you were beginning medical school.

WEISSMANN: I wrote about that in the new book *Galileo's Gout*.[8] I talk about it in relationship to prejudice against blacks. The first person to synthesize cortisone properly in the modern way was black, Percy Julian. I have an article called "Cortisone and the Burning Cross" and I described that year as the *annus mirabilis* because there's also the description of the LE factor, rheumatoid factor, and cortisone.[9] That was it. So there I was.

DAEMMRICH: Even as a first year medical student, you were aware of everything going on?

WEISSMANN: Oh God, yes. From my father, I mean, he was involved with the First Congress of Rheumatology.

DAEMMRICH: The film footage Hench had of the patient getting up, was that widely seen?

WEISSMANN: Yes. It was on Movietone News. I saw it at a meeting that my father took me to. Some of the first cortisone work was done by people named Currier McEwen and Joseph Bunim and at NYU and they talked about it at meetings in New York that I attended. It amazed me.

DAEMMRICH: Yes. Ralph [F.] Hirschmann's told me a little about some of this from the Merck & Co. perspective.

WEISSMANN: Yes, of course. I mean I think I have done some cortisone work. [laughter]

DAEMMRICH: Would you say that was one of the factors that pulled you into the research side as opposed to patient care or was it other experiences in the course of medical school?

WEISSMANN: No, I've always made clinical rounds. I've always seen patients. Frankly, when I land in many underdeveloped countries in the world, I'm the only doctor there I trust. I teach internal medicine, not just rheumatology. I mean I feel pretty good about examining hearts and EKGs [electrocardiograms]. When I was at Fort Dix, for example, I did two years of reading cardiograms. And so I feel pretty good about that.

But my love is science. I don't think there is the slightest bit of difference in value between the scientific judgment it takes to make a diagnosis, to treat a patient, or to judge how to put together facts in the lab. And, by and large, having trained people in both fields and people who have become professors in both fields—the good ones are good at both. It's just organization and imagination. The idea that scientists don't have the empathy or temperament for humans or that clinicians lack the rigor—at the extremes: at the fortieth percentile, probably correct, but at the sixtieth percentile, they're both fine and I respect them both.

DAEMMRICH: Understood. Once you finished the M.D. in 1954, you then had the Mount Sinai residency experience.

WEISSMANN: Right, but we called it an internship and you were on-call every other night, every other weekend, and you were paid twenty-five dollars a month. Then, after the internship, I had this conversation with Klemperer. Decided to cool it, join the army. I wanted to go anywhere in the world, but after Fort Sam Houston, where they shot bullets overhead for training, I wanted to be assigned to Frankfurt or La Rochelle[, France] or Japan. I didn't exactly want to go to the frontlines in Korea because the war was just over, but you could still be sent there. My friends who couldn't speak a word of German or French were sent to Europe. And they sent me to Fort Dix. My wife and I lived in Princeton, New Jersey for two years.

DAEMMRICH: Following that you did post-doctoral work with [Severo] Ochoa?

WEISSMANN: No. I went back to do another year of assistant residency at Mount Sinai and that's about the time I decided I really wanted to do science. The best rheumatology unit at the time, in terms of science, was being run by Morris Ziff at NYU, who studied rheumatic diseases. This was one of the oldest rheumatic study units in the United States founded before the American College of Rheumatology. Currier McEwen, who founded it, was an old Rockefeller University hand who brought in Morris Ziff as a bright young man.

So I thought I'd go to work in the NYU Department of Biochemistry with Ochoa, who had a connective tissue biochemist, Maxwell Schubert, working with him. Maxwell Schubert was the first person to describe that proteoglycans, such as cartilage or hyaluronate, were attached to protein covalently via serine ester bonds. So I chose to work there. Gangbusters,

you know; Severo was a European, intellectual, left-wing, Spanish Republican, and he was just a great man and everybody in American science came through his lab. About four months into my post-doc I was pipetting proteoglycans in a viscometer. If you treat it with either an enzyme that breaks down the polysaccharide or mix it with a countercharged protein, the viscosity drops. The time it takes to drop the viscosity level, that's the relative viscosity and you can measure the enzymatic attack on that by various things. So in comes Ochoa—

DAEMMRICH: And you're doing this timing with a stopwatch?

WEISSMANN: Yes, a stopwatch. Visual and stopwatch. Ochoa comes in with a distinguished visitor and says, "We'll be back and see how the tests came out." I say, "Professor Ochoa, can I show everybody what we're doing?" He says, "Anytime you're in my department you can show anybody anything. When I want to hide something, I publish it." [laughter]

I've always run my lab that way. I do not have any secrets. There have never been secrets in my lab. I've told everybody to tell everybody everything all the time. It's one community, somebody else gets it, big deal. If this is your one and only idea, you've got a problem. Those things you remember forever.

DAEMMRICH: It's a pretty witty comment. Of course it's saying once you publish the data, no one's reading it. It is effectively hidden. So you did a post-doc here and also a fellowship year at [the University of] Cambridge. Right?

WEISSMANN: I was working in the lab with Max Schubert when Lewis Thomas had been Professor of Pathology. He was appointed Professor of Medicine at NYU with only one year of clinical experience. He was, essentially, a terrific experimental pathologist and probably the most exciting person in modern biology at the time. He wanted his chief resident to be a person on track for a faculty job and to have a lab at the same time that he ran the division as a chief resident.

I was Lew Thomas' first chief resident at Bellevue Hospital. I had an office about this size [hand gesture] and I had a lab about that size [hand gesture] with people in it. They were technically working for Lew, but I ran part of the lab. He said, "Whatever you can do, go ahead and do. Continue what you're doing. It's your lab." And so when I was chief resident I had a lab and I continued some of the stuff I had been doing in Severo's lab. That was about the time Charles Weissmann was there, so there were two Weissmanns in NYU Biochemistry at the same time. In those days, the chief resident was on every night and I was off every weekend to come home.

DAEMMRICH: Just constantly on call.

WEISSMANN: Yes, I was constantly on call. Since I was there all the time, it was easy to do some lab work. We had some pretty good stuff on hypervitaminosis A and cartilage. Lew had spent a summer with Dame Honor Fell [at the Strangeways Research Laboratory, University of Cambridge] researching why excess Vitamin A reabsorbed bone rudiment and cartilage in animals. She and Lew worked for just a few months in the summer and realized the Vitamin A effect was related to Lew's previous work giving papain as an exogenous protease to animals. When given to rabbits, their ears fell down. At the time, when I was in biochemistry, I'd done the analysis of mucopolysaccharides—what happens when papain releases these from proteins. So both an exogenous enzyme and an agent that obviously did something to endogenous enzymes caused this phenomenon. Well how could this happen? So I went to Cambridge and here's another great story.

I arrived in Cambridge and I went to work on rabbits to see if, when you give them Vitamin A, you get the same rise in their blood mucopolysaccharide that you get when you inject papain. This is a breakdown of connective tissue. It's a model of arthritis, if you will, or joint destruction.

DAEMMRICH: Was the rabbit chosen because it has such a large cartilage based ear?

WEISSMANN: No. That is an entirely different story and that's also told in the book, *Galileo's Gout: Science in an Age of Endarkenment*. It's called, "The Case of the Floppy-Eared Rabbit." The Floppy-Eared Rabbits appeared in *Life* at the time and aroused national attention.[10]

I arrived in Cambridge and I wanted to do the same thing by giving Vitamin A to rabbits. Unfortunately, the professor of pathology at Cambridge had just died and he was supposed to sign the Interior Ministry documents needed for animal experimentation. Without that signature, I couldn't work on rabbits because I didn't have a license. So I went to Dame Honor Fell and I said, "Dame Honor, you must have a list. What's the lowest animal I could work on that doesn't require a license." She said, "Well you can work on tadpoles, but you can't work on frogs." I was pissed, and my feelings about animal lovers has remained constant.

Dame Honor Fell and I published the effect of excessive Vitamin A on tadpole larvae. It makes the cartilage undergo a premature metamorphosis, which led to the question, "where do enzymes come from that break down tissue?"[11] And that's how you get into lysosomes because [Christian] de Duve had just discovered them.

DAEMMRICH: It struck me in looking at some of the publications that the initial work was on this connective disorder, but also on the effects of removing cartilage and the impact of vitamins on cartilage.

WEISSMANN: The vitamin was simply a way of getting an exogenous agent to stimulate endogenous breakdown mechanisms. It was the vector. We now know that there are enormous steps involved and two or three pathways of tissue breakdown. But at the time, the idea of suicide sacs in lysosomes that burst open—now we know it's only one of the various mechanisms. At the time, tissue fractionation had just been devised. We did some of the first tissue fractionation studies.

DAEMMRICH: The fundamental understanding of what causes joints to harden was this sense that—

WEISSMANN: No, this isn't hardening. We were studying inflammatory arthritis. In rheumatoid arthritis, much of the damage is caused by inflammatory cells coming into the joint, not the resident cells. In osteoarthritis, it's the resident cells and oxidative damage, et cetera—wear and tear. Joe Namath's knees or a ballerina's toes as opposed to now that I'm in my seventies, when I have tennis elbow from wear and tear. To make a long story short, this was the first time we had the idea that cartilage could be broken down by endogenous agents as by Vitamin A and by exogenous agents like papain. The model for that was rheumatic fever, where the streptococcus makes a papain-like enzyme. We thought that was how all tissue damage came about. In some circumstances, endogenous enzymes from the cartilage cells themselves break down tissues without an influx of new cells.

DAEMMRICH: Walk me through a little bit of the transition, then, in your research from that body of work to looking at lysosomes and the lipid structures. I guess it coincided also with the move back to, and then an actual professorship at, the NYU School of Medicine.

WEISSMANN: The papers flow very nicely into each other. We made fractions first of a liver and got a lysosome rich fraction using appropriate enzymatic and biochemical assays. This was in the days when you did all of this by sucrose gradient centrifugation and ultracentrifugation of the molecules themselves. Getting stuff out all by yourself and a lot of hard work.

It is a very simple research method. Bunny A, Bunny B. Bunny A has had Vitamin A or endotoxin and Bunny B has not. Whip out their livers, or if you want, you can examine their ears, but whip out the livers. Grind them up with 0.25 M [molar] sucrose in a Pasteur homogenizer. This keeps them intact so that the sucrose can balance the osmolarity on both sides of the membrane. You get large granule and small granule fractions. Large granule fractions are the lysosomes or the fragile vacuoles in them and then you add various agents to

them from the outside to see if they become labilized or stabilized. A paper by that name, "Labilization and Stabilization of Lysosomes," a review that I wrote in 1964: it made a big stir.[12] The idea is that the cortisone and chloroquinine are good for membranes and rheumatic diseases: these stabilize lysosomes. Then things that were bad for rheumatic diseases like Vitamin A or streptococcal toxins, labilize lysosomes.

I heard a lecture in 1964 at the New York Academy of Sciences by a man who subsequently became one of my closest friend, Alec [D.] Bangham. He was doing lipid monolayers and adding things to them to see how toxins or detergents perturb these. I said, "A-ha." That's why I went back to Cambridge because I knew where he was working and I loved Cambridge. Besides, I've never spent a summer in New York. In the 1960s, I always went back to Cambridge. I only started coming to Woods Hole [Marine Biological Laboratory] in the 1970s. In the 1960s I spent a few months in Cambridge every year. I had been in Cambridge [for summers before at Strangeways] with Dame Honor Fell and now to work with Alec. In 1964, the summer of liposomes, we explored lipid structures and had decided that a monolayer really isn't very good. Alec had already described the fact that you could make structures that sequestered ions.

DAEMMRICH: Was that his electron microscope work?

WEISSMANN: Yes, exactly. It was just a negative standing with Bob Horne, but the functional work was rudimentary. Alec had learned a little bit by doing sodium trapping, learning that vesicles trapped ions differentially. We used an old-fashioned flame photometer to see what leaked out of them.

By the time I got to Cambridge, which was the summer of 1964, I said, "Let's pretend they're lysosomes and we'll try to put something inside and see if it leaks." We did that with trapped potassium and sodium, and so on, and we found that the same agents that ruptured lysosomes, e.g. streptococcal toxins, and cortisone, which stabilized them, would have the exact same effect in the multilamellar lipid structure. That appeared in the *Journal of Molecular Biology* in March of 1965 and the rest is history.[13] That led eventually to putting an enzyme in there for the first time, which we did in 1969 or 1970. It was the first time any big molecule had ever been incorporated in a model membrane. In the summer, of I think 1973 or 1974, I was teaching in the MBL [Marine Biological Laboratory] Physiology course [at Woods Hole]. When the whole physiology course did the experiment, we first targeted the liposomes. We put immunoglobulins around the liposome. By that time I'd done my neutrophil work and knew that phagocytic cells loved immunoglobulins. They had receptors for them and if you could target those, my God, you could get into cells! First, it was trapping sodium, then trapping an enzyme, then coating, and so on. If you can do that, why you might even be able to have a company that gave drugs that helped people.

I must say, the work followed a narrative flow beginning with the question of what kinds of things will injure connective tissue as a substrate—endogenous and exogenous agents? Then,

where are the endogenous materials sequestered? Answer: lysosomes. How do they reach the exterior? Answer: neutrophils secrete their content of lytic enzymes as they eat. In other tissues, a process called "autophagy" takes place and cells eat themselves up.

DAEMMRICH: You then published a series of articles; the studies in lysosomes start in 1962. Did you plan that whole sequence of articles out? The first one is, "Studies in Lysosomes I." You obviously knew there was going to be more than one.

WEISSMANN: It was based on de Duve's series on tissue fractionation numbered one, two, three, four. I got to know and admire him (he is also a very good tennis player). I knew I'd be working on this lysosome stuff for awhile.

DAEMMRICH: Had you mapped out what the whole series would be?

WEISSMANN: No, but I knew that I'd be working on it for awhile. By the time I wrote one, I was on two, and then three already. When you do science, while you are writing the one, you're doing the next and so on. All of those studies on lysosomes, by and large, were based on the de Duve model of tissue fractionation. I didn't get into the true cell biology or the electromicroscopy of how secretion takes place till much later. No one knew what the mechanism of secretion was. That came later. That was the 1970s. The 1960s was primarily studies in lysosomes. Not until the 1970s did I become a cell biologist. I had one of the few electron microscopes in a hospital and my lab did its own electron microscopy.

DAEMMRICH: Maybe I honed in on this not wholly accurately, but 1965 seems to be a seminal year. The number of publications was going up and that's the year people like to identify as the time when the lipid bilayer of the cell wall was understood.

WEISSMANN: I don't want to make an extravagant claim, but I'm about to do so. You didn't know that the bilayer theory was correct until you made it, showed that it enclosed a macromolecule, and that it behaved like a cell. And when the *New York Times* wrote this up, as we first presented it, they wrote "scientists create part of a cell."[14]

The part of the cell that we created was a sort of living thing: namely an enzyme lysozyme, that was separated from its environment by a lipid bilayer. We knew the structure and we could perturb that structure. That was in the *Journal of Molecular Biology* in 1965. We added two substances to that bilayer. One had the A-B ring junction of the steroid *cis* and the other one was in *trans*. By just changing that *cis*/*trans* conformation, you could either labilize or stabilize the lipid structure. *Voila*. That's the equivalent of double helix. A functional cell membrane of course is not only lipid, and a functional gene of course is not only DNA.

I would say this for lipid membrane structure: Davson-Danielli model or the Singer model were important in establishing membrane theory. But, in terms of pure testing of that hypothesis, the liposome was it. It was the 1965 paper which showed that the manipulation of that structure would mimic that of the natural membrane. The natural membrane was a lysosome. We studied a lysosome in one dish and a liposome in the other and they had the same properties. We had a plot of concentration of steroid and structurally similar structures. All that was different was the structure of the steroid that we added.

DAEMMRICH: Were there competing theories at the time for how the cell wall structure looked?

WEISSMANN: Absolutely. In fact, when I presented this, I wanted to have a grant on liposomes in 1966 or so and George Palade came to site visit my lab at Bellevue and he said, "No, these are just phase transitions you're studying." People didn't accept liposomes as an interesting topic. But now they are as accepted as hydroxyapatite. They are there. By the way, you know, I coined the word and I'm in the *O.E.D.* [*Oxford English Dictionary*] for that.[15] So that's my claim to fame.

DAEMMRICH: If all else disappears, we know the *O.E.D.* will be there.

WEISSMANN: That was coined at a pub right near Cambridge. [laughter] Alec Bangham and I were having a discussion. I said listen, "Lysosome, liposome." And he said, "You're on. We'll call it that." And a few years later journal editors permitted use of the name.

DAEMMRICH: Where did the lipo- come from?

WEISSMANN: Lipid. Lipo-, lipid body. I know enough Greek. That's why idiots call it a liposome [long i-sound], but I say, "Tell me, do you call it liposuction [with a long i-sound] or liposuction [short i-sound]." [laughter]

DAEMMRICH: Were there also competing methods for doing this set of laboratory work?

WEISSMANN: I must say, at the time there were—for example, Peter Lachmann and [Robin] Coombs at Cambridge were working on complement lysis and Steven Kinsky was working on complement lysis and lipids and he was interested in Dourmashkinin London was working on lipids and complement and did negative staining and that was interesting. Additionally, Lampen

was interested in the cholesterol dependence of amphotericin action, but he wasn't working on liposomes. Then others began working on liposome structure after we described it. It couldn't be done before that.

I've never actually felt competition in anything I've ever done. There've been people who've worked in adjacent fields and become very good friends such as Steve [Stephen A.] Malawista at Yale [University School of Medicine], Charlie [Charles G.] Cochrane at the Scripps [Research Institute], and Edgar Pick of Tel Aviv University in Israel. Sure, there are people doing things before me or after me, but I have never felt competition. I must say that Frank Austen's group, who were working on cyclic-A and cyclic-G enzyme secretion, has beaten me to many punches. Still, no, I have never felt competition.

DAEMMRICH: Tell me in a little more detail how the encapsulation worked?

WEISSMANN: In Cambridge in the summer, if you wanted to see whether something came out of a lipid structure, you got the lipids on a Sephadex or other sizing column, you ran it through by hand, as we did in that lab here at MBL in the 1970s. It's all done by hand. You had the stuff that was in the lipid separated from that which wasn't. Then what you did was you analyzed sodium in the fractions or—and or dyes—or if you had a sodium ion, you just dialyzed it. What came out of the bag was… it came out of the membrane and I figured that wasn't terrific. That was ok for sodium ions or dyes.

I worked out column separation for a protein and I figured that we had to have a small protein, crystographically defined. I knew exactly that it was a globular protein with cations all around it. Lysozyme has eight positive charges per mole. So if you make cationic liposomes, any trapping can't be electrostatic. As you increase the amount of cationic charge on the lipid bilayers, which are multicentric, the aqueous space, the V_{H2O} increases and so Sessa and I had to show, number one, that the enzyme was latent, that you couldn't assay it in the presence of substrate and number two, that the amount you trapped was directly proportional to the V_{H2O}, the space available for trapping. We wrote the equations for this.[16] And then we did a lysozyme column by hand. Grazia Sessa, who was my technician, was extremely helpful in creating this breakthrough in terms of trapping a macromolecule inside a liposome. And then later here at [The Marine Biological Laboratory at] Woods Hole the other breakthrough when we accomplished was the targeting, by means of ligands, immunoglobulins. Since I'm a rheumatologist, I'm glad it was via Fc receptors.

DAEMMRICH: That's interesting. If you look back on it now, what would you say were the longer term impacts of that set of research in the 1960s for your overall career? Was that a defining moment?

WEISSMANN: Well, let's put it this way. I think in terms of utility to humankind—at improving the human condition—I'd say several million people have been treated with agents involved in liposomally delivered drugs or other lipid-based products. I have said it's my biggest contribution. Understanding rheumatoid arthritis via immunoglobulins and complement could have been done by anyone else, and knowing the exact mechanism of how that works thrills me. But I think my real contribution is: if it goes in a vein and helps somebody, that's what a doctor's supposed to do.

Another thing that we discovered that people don't talk about much, which is becoming exciting now is the whole theoretical idea of antioxidants in blood. We discovered that ceruloplasmin is a major defense against oxygen-induced injury.[17] Do you know of Wilson's Disease where the patient gets fibrosis of the liver and CNS [central nervous system] damage because the free copper is deposited in tissues. Copper is nothing but a catalyst for free radical formation and that's why you get brain damage and dopamineryic neuronal death, et cetera, just like in Parkinson's disease. In liver disease, fibrosis, which is produced by ionizing radiation or your own oxidizing radicals, we discovered that the major antioxidant protein in our blood is ceruloplasma. And we did it by using liposomes and techniques we devised to measure leakage of sodium or glucose. We just saw the effect of ceruloplasma. I think it's a big discovery and everybody's excited about it again because of free-radical induced hyperoxia in cells.

DAEMMRICH: As I was reading through your publications, it struck me, there's a shift, or a direct lineage, in the 1970s towards looking at issues in signal transduction?

WEISSMANN: Another great Woods Hole discovery story. I'm up here teaching the Physiology course and I'm having students target liposomes in dogfish, which don't have peroxidase. Meanwhile, in the 1970s I'd gotten interested in prostaglandins. That's how I met my two best friends in Europe, John Vane and Bengt Samuelsson at prostaglandins meetings. I left the prostaglandins on my lab table, in vials, with Bob [Robert B.] Zurier, who is at [the University of Massachusetts at Amherst] now. They were simple experiments. He'd been adding stuff to neutrophils to see what made lysosomal enzyme secretion go up or down. I said "add cyclic A," it's a secretagogue signal that had been shown in parathyroids—[Earl] Sutterland discovered that cyclic A signal made the several glands secrete—so I said add a little, because neutrophils secrete and so on like that and see what effect prostaglandins have. It's the same thing because they must respond to cyclic A. There were only three [types of prostaglandins], PGF_1, PGF_2, and PGF known. They'll do something like cyclic A.

I was working on a liposome column. I get a call from Bob Zurier and he said, "Listen, I've done these experiments over. Gerry, you're going to hate me, but cyclic A and prostaglandins turn them *off*!" The inhibitory effect of cyclic A on neutrophil secretion and activation and—prostaglandins of the E-series inhibiting this—shows that prostaglandins were modulators rather than mediators of inflammation. Then, of course, how do they share induced signals via cyclic A, A kinase—we described the first cyclic A and C kinases in neutrophils. Then we did the cell biology of this: how do the kinases effect the trafficking of granules along

microtubules? And that work was done with Sylvia Hoffstein, electromicroscopically. And so, agents that raise cyclic AMP inhibit, those cyclic GMP, enhance enzyme secretion. And that's how cholinergic agents work and why I have gotten to be friendly with Jean-Pierre Changeux, who worked on the structure of cholinergic nicotinic receptors.

Basically once you're involved in studying how lysosomal enzymes are secreted, you are committed to work out the signal transduction mechanisms of secretion.

DAEMMRICH: At this point, what was your research vector? What cells, what organism model are you working with?

WEISSMANN: In the winter, the only cells I've ever worked with are—after I did the bunny experiments—are neutrophils. Eric Kandel has reduced the brain to *Aplysia*. He reduced the central nervous system to defined neurons and *Aplysia*. I reduced inflammation to the neutrophil, the white cell. It's always the first cell present in inflammation. I figured if you understand them, you understand everything else that goes on. Of course that's not entirely true, but it was in keeping with the principle of reductionism, as with liposomes.

That's a reductive hypothesis. And since I'm a fan of the eighteenth-century Enlightenment, I believe in *reductio ad profundum*. I think that if you can't reduce it you're not being a scientist. On the other hand, if you can't then generalize, your reduction isn't very helpful. But that you do first. We reduced inflammation to how white cells secrete their enzymes to the outside, what makes it free radical, and how this gets turned on.

The most cited paper we've ever written is the one in which we show that complement, not the whole sequence, and immunoglobulin, and not the whole sequence, will turn on white cells in the absence of their eating; not just phagocytosis which they're supposed to do.[18] That means neutrophils have receptors and that these receptors signal differently. So IGG receptors signal via one pathway, and complement receptors for C5A work via another. But you had to work out the signal transduction mechanism in both and then you figure out how colchicine works on one pathway, while steroids work on another.

DAEMMRICH: Right. You could describe that work at one level of understanding the core biological mechanism. At what point were you also becoming interested in the druggable targets?

WEISSMANN: I think always. The *Journal of Molecular Biology* paper has data on cortisone and other membrane-active steroids where we've showed the differential structures. Diethylstilbesterol is very disruptive while estradiol is protective. And steroid structure is very important. Cortisone is always protective: indeed the first paper I ever did with John Dingle on

isolated lysosomes when first made, we shone UV light on the organelles because people with lupus are made ill by UV light.[19]

DAEMMRICH: I didn't know that.

WEISSMANN: Sure. UV light induces apoptosis in cells. It produces free radicals. People with lupus have to stay out of light and cortisone cures them, literally. I've always thought of experimental medicine as telling us how drugs that we know work, really work. You know, there are literally three aspirins, which is another one of our contributions to the field. If you give aspirin for rheumatology, you're going to have to give five to six grams a day in order to be anti-inflammatory. I take an aspirin every other day just so I don't get a coronary or a pulmonary embolism. And, if you don't want a headache, you take two every four hours. So we've got three different modes of action. By finding out the mechanism of drugs you already know work, you are able to understand them much better. If you just have a target, you might not have the proper structure-function relationships. But if you already know what works and what doesn't you get proper controls. Tylenol, for example, is not anti-inflammatory, so use Tylenol as a control in aspirin experiments. It's that kind of clinical observation that has been very helpful in the lab. And I've argued many times that a medical school education is, for a scientist, the equivalent of a liberal arts education for a writer.

DAEMMRICH: Because if you can't think more broadly about body systems—

WEISSMANN: It permits you to think. It gives you more clues and many great Ph.D. scientists have gotten that from the study of biology in general. But the tactile knowledge you get from examining patients and the emotions involved in worrying about patients makes you think about how things in general are working. And that desire for insight becomes personal.

DAEMMRICH: This is slightly out of chronology, but what was the response within the rheumatology world to the COX-2 inhibitors? Specifically I am thinking of Merck's Vioxx, the market appearance, and then the high profile withdrawal of this class of drugs.

WEISSMANN: I think COX-2 inhibitors are very good drugs. I'll make a long story short: they're fine drugs when given for the appropriate indications, but they have clear cardiovascular side effects. I would have expected such side effects, but not quite as significant as they turned out to be. That has to do with our view of prostaglandins as regulatory. Different classes of prostaglandins do this in different tissues. But the reason the situation with these drugs got so bad is that you shouldn't advertise drugs to the public. You advertise to the public, you'll kill them. Consequently, one hears of people asking for erythropoietin [EPO]. Patients should not be asking their oncologist for this, your oncologist should tell you whether or not to use Epogen.

This Vioxx debacle is a perfect example of doctors being made to prescribe these drugs over long periods of time rather than for short bursts of time for the proper indications.

Unfortunately, in order to increase their market share, most pharmaceutical companies are run by people in marketing, or in legal, or in accounting, rather than science. When Bill [William C.] Steere [Jr.] was running Pfizer it was a great company because he knew the science. It's also true with a number of others. I think Roy Vagelos is one of the great men in American science and was a true pharmaceutical innovator. But now, in the concessions of the pharmaceutical industry to marketing needs are going to wind up killing a lot of good drugs.

DAEMMRICH: Because it's shifting people's concept of risk?

WEISSMANN: Of course. Nobody listens to the warnings: "tell your doctor if you have an erection lasing more than four hours." People giggle. But that's not the real side effect of [Pfizer's] Viagra. The side effect is that you can go blind. Anyway, the response of the rheumatology community is fury at advertising.

DAEMMRICH: Now a therapy that, in the right hands, could have been used effectively disappeared from the armament. It's sort of a tangent to where we want to go, but did that set of research nevertheless stimulate some interesting work?

WEISSMANN: Not the stuff I've seen. The COX-2 story is very good now in terms of tumors. COX-2 in different tissues will give you different end-product prostaglandins, some of which turn off inflammation, and that may be beneficial. So they were two defensive responses to cytokines, which in some cells may be tumor-provoking. But by turning down the defense mechanisms, you get a cardiovascular event. We discovered why COX-2 inhibitors are lousy for you. Basically, some prostaglandins are anti-inflammatory and that anti-inflammatory effect in blood vessel atheromata is not good. That has not been rigorously tested but I'm confident because of the number of papers suggesting that.

DAEMMRICH: Let me jump a little. In 1973 you became director of the School of Medicine's Rheumatology Division at NYU. What kind of responsibilities did that mean in the shift from professorship to director?

WEISSMANN: Well, from the moment I started as a chief resident, I have made clinical rounds at Bellevue Hospital teaching internal medicine. Becoming director of rheumatology meant having rheumatology fellows to train. At the time, it was the largest rheumatology service in the country with a huge patient load. We had Bellevue Hospital, the Manhattan Veteran's Affairs Medical Center, and [NYU's] Hospital for Joint Diseases. We've trained

about a third of the rheumatologists in the New York area. Many of our graduates are distinguished professors and, of all the medical divisions at NYU, we've always ranked highest in *U.S. News and World Report*.

DAEMMRICH: This is a naive question. Does every teaching hospital have a division of rheumatology?

WEISSMANN: Yes. As with pneumonology, nephrology, hematology. It's a subdivision of internal medicine.

DAEMMRICH: In the time span of your career, what kind of growth curve has rheumatology been on?

WEISSMANN: I'd say rheumatology has been on an arithmetical increase, whereas procedure oriented disciplines have expanded logarithmically. Gastrointestinal physicians or cardiologists have new techniques they can employ where you're much more heavily remunerated. Rheumatology still is more cognitive than procedurally oriented.

DAEMMRICH: It requires a different skill-set for understanding the patient.

WEISSMANN: I'm, deep down, a social democrat, which means I've got the Marxist prejudice of asking and *cui bono*? Everything has been shaped by economic forces. A lot of rheumatology work has been outsourced to imaging now and many other specialties because they are remunerative: there's a high overhead of reimbursement.

DAEMMRICH: When a patient came to you in the mid-1960s and complained of joint pain, how did your analysis, testing, and decision on a treatment routine change compared to the 1970s, compared to the 1980s?

WEISSMANN: I think there's been a good arithmetical increase of precision in diagnosis. The big jump came between 1965 to 1975, but not much since then in terms of precision. Since then, just a lot of buffing. But in terms of what we can *do*, it's been very significant. Since I was trained in rheumatology when I first learned about it, we've gotten rid of gout as an interesting problem, although the mechanism is still unclear. We then wrote a paper called "The Molecular Basis of Gout," which essentially details crystals interacting with lipid membranes.[20] Well, that's one of the mechanisms. There are others.

DAEMMRICH: But the way to get rid of it is a drug treatment.

WEISSMANN: Completely. We've gotten rid of gout. We don't have rheumatic fever in advanced form anymore and we don't have tuberculosis. Those three occupied the bulk of rheumatology inpatient services when I was young. Rheumatology in hospitals right now is lupus, periarteritis, and adult scleroderma. Outpatient, it's back pain and for the wealthy, sports injuries. And that's what I practice here at Woods Hole with my friends.

DAEMMRICH: Let's move ahead. Let me ask you a little bit about your experience with The Liposome Company.

WEISSMANN: Eighteen years in American capitalism.

DAEMMRICH: What were the origins?

WEISSMANN: It began on a flight from Moscow[, U.S.S.R] to New York, on Pan Am [Pan American World Airways], with one stop in Copenhagen[, Denmark]. I was part of an international delegation with a number of distinguished scientists asked by the Russian Academy of Sciences to look into the relationship of food metabolism and intercellular organelles.

DAEMMRICH: This was an external review board they had invited in to oversee their scientific work?

WEISSMANN: Exactly. There were some people in Russia who picked up some liposome stuff, so I think this must have been 1978. Everyone was thrilled to get out of there because this was during the [Leonid Ilyich] Brezhnev era. They took your passport away and gave it back when you were leaving. I finally got my passport and heard the great American voices of the Pan Am stewardesses. I just thought, "Oh God, I'm out of this thing." Then the pilot made an announcement saying, "Ladies and gentlemen, I have something to tell you. We have four engines. One of the engines has some problems with it. But we decided not to have it fixed here. We can easily make it on two engines to Copenhagen. We've got three. I hope you'll agree with my decision." He was very reassuring and we all applauded.

We took off and landed in Copenhagen. During the layover, there was a guy in the front, a short guy but very peppy with a very nice looking wife, and he introduced himself as a trustee of NYU, [Edwin C.] Jack Whitehead. He said, "Hi, I'm Jack Whitehead. How are

you?" We started talking and I told him what I was researching. A year and a half later he and another guy showed up at my office at Bellevue with a venture capital proposal involving drug delivery through cellulose particles. I said, "Well I'm not in biotechnology. I know little about this, but let me tell you what I know." I spent about an hour and a half and he fell in love with the notion of liposomes.

He was an American entrepreneur. I met about two people like that in American life. One is Larry [Lawrence J.] Ellison and the other one is Jack Whitehead. They're just larger than life. They're like the character Undershaft in [George Bernard Shaw's play] *Major Barbara* or [the title character from Henrik Ibsen's] *John Gabriel Borkman*, the progressive capitalist.[21] They are people completely open to innovation. Every idea is theirs to make possible. Spectacular. Both are broadly cultivated with a deep appreciation of the arts and they were people in whole, men in full.

I remember distinctly Jack wanted me to start the company and become his chief scientific officer. I said, "Jack, my parents didn't raise me to be an industrialist." We were down in the tap room of the Century Club and he was trying to ply me into doing it with drinks. But I still said no. So we got Mark Ostro who had studied liposomes with me to become the first officer.

I then did something that I don't think is done by too many people in biotechnology. Take a look at my bibliography. I have not done one biological experiment on liposomes since The Liposome Company was founded. None. Any biological ideas I had were done on their time and in their place and with me only as an advisor. But nothing in my lab was either funded by the company or could have a direct bearing on anything going on there.

DAEMMRICH: It's interesting you anticipated a question I had written down here, which is how did you strike a balance between work in the startup firm and your academic position? I think you just answered. There was a wall.

WEISSMANN: And an internal firewall. I made it very clear to everybody in the lab also. We had done enzyme replacement experiments and we stopped doing that the minute the company started. Then of course you have to have a business plan and, of course, like all business plans, it was a pipe-dream. What we planned to do was to put antiviral drugs in liposomes.

DAEMMRICH: Right, encapsulate them? How would they be delivered to the body?

WEISSMANN: Aerosol.

DAEMMRICH: Inhaled? At the time, in the early 1980s, what kind of aerosol drugs were out there?

WEISSMANN: Almost all the anti-asthmatic and the steroids were already aerosolized. And it was a long experience of what could be done, what can't be done. We learned who goes into industry and startups, what kind of personnel you get, who you hire, et cetera. My experience in the business end of biotechnology is a big plus/minus. However, I again quote Jack Whitehead, who once said, "You know Gerry, what the difference is between academia and business? In business," he said, "Gerry, it's dog eat dog. In academia, it's the opposite." There's an awful lot of finagling both in terms of the science and in terms of market handling and presentation. I don't think I could be in the business side of it. It's tough enough being in academia, which is why I've never thought of any administrative position. I just don't do that. I also know what it's possible for me to do. Consequently, I prefer the situations where you can avoid committees.

DAEMMRICH: What was your role then in The Liposome Company?

WEISSMANN: We collected a very nice bunch of scientific advisors and Bengt Samuelsson, was also on board—he's been with me on most everything—and Rudy Guliano, who is a very fine guy, and John Weinstein, and Carl Alving. We advised the Company on their projects. But the people who ran the company, ran the company. We criticized the science and suggested things that they might be doing. And we had some unbelievable successes and some believable failures. Our market value was up to a billion or so dollars and then we dropped down when a prostaglandin anti-inflammatory project didn't work out because the pharma people insisted we had to try it on "systemic inflammatory syndrome." I thought you ought to try it on lupus patients first, but there wasn't enough of a market.

So again, that's the way companies work. I learned a great deal about business. I don't think we could do without it. I'm a fan of pharmaceutical development and biotechnology. But I think we could do it better and with more idealism. I think the FDA [Food and Drug Administration] is a disaster because of its policy of approving a drug for one specific *particular* indication. It may be the worst thing that's ever happened to drug development. Drugs should be approved for syndromes or conditions, for example, inflammation. Cortisone, what are you going to apply it for, for a superficial wound? It also works in asthma, in lupus, and also for brain injuries. But, you see, you've got to get it approved for one indication. Well, that doesn't quite hack it.

My own feeling is that after a good phase two [clinical trial] in one kind of condition, you ought to get the drug on the market and see what happens in the real world. You won't have these recalls. There will be toxicities, but that's how drugs are developed in the first place and very successfully. But litigation, of course, is the worst part of that. Oliver Wendell Holmes Jr., the jurist rather than the doctor, wrote a book called *The Common Law* after coming

back from the Civil War.[22] Holmes argued that the law is what the courts decide and I'd like that idea applied to pharmaceuticals after safety, dosage, and a good phase two. These double-blind phase three [clinical trial]s bother me because the exclusion criteria make it clear that you're going to miss the real side effects. Also the single indication criterion makes clear the error. Who would have thought methotrexate for rheumatoid arthritis, an anti-folic acid? Chloraquine, you use that for malaria. Well, it works anyway.

It's one of the things I learned. The other thing I've also learned is that the American system of quarterly reporting puts an enormous strain on American business. It emphasizes a secondary, tertiary, and quaternary interest. I don't think anybody should ever be allowed to sell short. Permitting large funds to sell short is the Guantanamo Bay of American capitalism. It's a dirty downside because the function of capital is to raise capital, not to make money off of somebody's disaster. If you allow hedging, the market doesn't create capital. So they say you need hedging to keep companies honest. Nonsense. Value alone will do that. Anyway, in the old days funds were never allowed to sell short. But my business years were a very educational and a very impressive experience.

DAEMMRICH: It does seem like two products were developed: Abelcet and Myocet. Right?

WEISSMANN: Yes and that's doxorubicin [with the trade name Adriamycin] and liposomal doxorubicin [with the trade names Caelyx and Myocet], its all over the world, and Abelcet, which amphotericin lipid assemblies, is terrific because it is not only used for fungal diseases. Last year I think Enzon Pharmaceuticals, who we turned it over to, made something like thirty-two million dollars on it, so that over five years is a lot of money.

DAEMMRICH: So tell me, if we can focus in on that case just a little more carefully. Did Liposome's Abelcet get all the way through to FDA approval?

WEISSMANN: Yes. And it was based—amphotericin liposomes came from my paper in the *Journal of Biological Chemistry* on amphotericin and liposomes.[23] Doxorubicin was brought in because, according to Christian de Duve, it was a lysosomotropic. But the technology of making something like a liposome on a pharmaceutical level was done in our factory in Cincinnati[, Ohio]. It went through FDA approval and clearance. I learned how these things are done.

DAEMMRICH: And you have good manufacturing inspections.

WEISSMANN: And good manufacturing practices. There was a lot of sampling. How do you say this isn't just a molecule, it's an assembly and people on our board had had major

experience in this. I mean this is an enterprise. It's a ship. I'm just wildly impressed by that part of it: the technical part of making drugs—understanding and making sure they're clear and that it done soon; that kind of special expertise is one of the great things in American industry.

I'm just wildly impressed by it. That is better living through chemistry. [laughter] It's pure chemistry and mechanics, mechanical engineering. It's the western genius at his best. I'm wildly impressed. When you see the first bottle coming out and there's stuff in it, never mind *The Journal of Biological Chemistry*, never mind this paper. When it is in a bottle and the label is on and it says The Liposome Company. Oooh!

DAEMMRICH: It's no longer a small scale laboratory job.

WEISSMANN: Exactly. The two thrilling experiences that I've had in that industry is 1) seeing that first bottle, and 2) seeing LIPO on the NASDAQ ticker. Not to mention the fact that a company does job creation, its part of industry, and all those parts—you can't write [Karl Marx's] *Das Kapital* without capital.[24] It's hard to be a Marxist without capital, which is what the Russians forgot.

DAEMMRICH: One analysis of what happened to the Soviet Union is that they went from a pre-capitalist to post-capitalist country without being capitalist in between. Are you still involved in the company?

WEISSMANN: No. The company was bought out by an Irish company called Elan Corporation. Then they sold the two products to different areas and they do other things now.

DAEMMRICH: This is how Myocet got the European approval and is sold by Zeneus Pharmaceuticals and the Abelcet was spun off to Enzon Pharmaceuticals?

WEISSMANN: Exactly. The company dissolved and I've never owned stock in anything since. I just don't own stocks. But I was given Liposome shares, I held on to them, and that was it. I'm still fascinated by the biotech business and a lot of my good friends are in it. We have meetings in New York to discuss it: I love the hunt for the new. There's great stuff coming out all over that's adventurous and marvelous. But all the same, I'm glad I'm out of it because eighteen years is enough.

DAEMMRICH: You said that you've avoided becoming a manager and have avoided committee work. Yet 1985, you were convinced to join the Advisory Committee to this startup effort by The Pew [Charitable] Trusts Biomedical Scholars program.

WEISSMANN: It was not a startup effort by the Pew Trust that got me on board, it was Josh [Joshua] Lederberg calling me up. I will do anything Josh asks of me. I think he's the single most intelligent person I have met in the universe and I've met a lot of them. Breathtaking, just breathtaking! The proof of that is: when he subsequently asked me to do the second one, the Ellison Medical Foundation, I did that also.

When Josh called me about the Pew, he talked about the people who would be involved, et cetera, et cetera, and every one of them was a "wow." It was that group that picked the first person to do the oral histories, Eugene P. Kennedy of Harvard University. He is a close friend of mine here, indeed our families have played charades together. He is a great American biochemist who works on lipid biosynthesis. Everybody in the group thought he'd be perfect.

DAEMMRICH: He did an initial set of oral histories and then Pew decided the oral history program was getting bigger.

WEISSMANN: Exactly. And besides, he was a scientist. You need to be a professional to do this: oral history stuff is not his sideline. First of all, your own person is too much involved. I have a lacuna large enough for Wisconsin Swiss Cheese that I just know nothing about, or won't talk about because I have problems deep down inside about that. You can't be an objective reporter and always ask an important question.

DAEMMRICH: One thing we've seen when scientists interview each other, particularly if they're in the same field, is that they're speaking so much the same scientific language that it's a wonderful oral history. Except no one can read it because it's too technical; you're lost in it. There needs to be a balance between the science and everything else.

WEISSMANN: Yes—the important thing is never, if possible, to use an abbreviation.

DAEMMRICH: Right. [laughter] So Josh called you up and said, "I'd like you to come do this." What else did he tell you about the Pew program from the start?

WEISSMANN: Well, you know, it wasn't exactly clear as to how we were going to pick the scholars and what the criteria should be and so on. I think my contribution to the early discussions of the group was not to worry so much about the scholar's CV.

DAEMMRICH: I'm showing you the Advisory Committee members in 1985 when it was formed.

WEISSMANN: Well, let's put it this way. At the time it was formed, I knew Bob Berliner and Robert Berne, well, and I knew Jean Wilson very well. In this group, I knew everybody well. Mattie [Matthew Scharff] was a student of John Uhr's, of John Uhr and mine at NYU. We were house staff together at Mount Sinai. Alex [Alexander Rich], I got to know through the Pew and we've been close friends since. Bill [William] Paul was at NYU when I was. So I know most of the people. Berne, by the way, lived right over there, two houses from me at Woods Hole, and we were tennis partners together. We played doubles against other people like Gene Kennedy and Art Pardee. If you take a look at the beginning of the Pew, Josh asked a number of people who are clinical scientists, clinicians who saw patients. Bo Berne, who is a physiologist, is an M.D. Bob Berliner was. David Sabiston's a surgeon. Mitchell Spellman I never knew. Jean Wilson is an M.D. and I am, of course.

So it was a more clinical group than the later groups of Pew Advisors. But it began to be more oriented to pure science as things came in. For example, the Harvey Society, it also trended that way. For that matter, most of the founding members of the Royal Society were physicians and then pure science took over. That's happened again and again and I have no feelings one way or the other.

My contribution to this group, I think, was to simply say, "Let's forget about the recommendation letters and all of this stuff because I'm not sure about letters. Ask only one question. What's the discovery?" What's the discovery and does it sound as if there was a real contribution made by this person? That's all that mattered rather than the number of publications. And most people agreed. I also thought what was lovely about the group was that it wasn't an NIH [National Institutes of Health] review panel who worry about details like: "Oh my God, we can't do it with that buffer." It's just an application, not a discovery.

You knew very well that recommendations frequently tell you as much about the recommender as about the recommendee. When somebody you know who is a real son of a bitch says, "wow," you pay attention to that. That is, of course, if the candidate is among the top 5 percent, but if everybody's recommended as "the top 5 percent" then you pay no attention. The other thing was that the original idea of limiting the applications to certain institutions is important, terribly important.

DAEMMRICH: Where did that idea originate?

WEISSMANN: Among a few of the people there. Again, it's unabashed elitism. If you'll notice, the Ellison works the same way. That was Josh's idea and a number of other people as well. I think if you don't begin by limiting applications, you're flooded by crap. Consequently, you have too much work to do to limit the candidate pool. There's no reason not to have a

prescreening. Granted you'll make errors and you'll leave some people out. But this is one program in one area and I think unabashed elitism has not hurt the Swedes, the Brits, and the French relative to us. They get more bang for the buck than we do by not giving out research money geographically, politically, ethnically, and gender based. The nice thing is that nowadays, since there are so many non-Americans who do their research in the U.S., you get more variety, whether the money goes to men or women, I love it. The other unique thing about the Pew process is no interviews. I remember people having been interviewed for one or another grant or so on—that's ridiculous. They need to have discovered something or they haven't. It's not about good table manners.

DAEMMRICH: Was the Pew program only going to fund younger scientists from the start?

WEISSMANN: Well, you could have done a lot of things. For example, with the Ellison we have two levels. But the Pew is the basis for the Ellison program, because it's still Josh's idea. For the Pew we decided younger scientists face a critical time when people need support and this funding permits real independence. That was the innovative aspect.

DAEMMRICH: When you think of funding in the biomedical sciences, you immediately think of NIH and other large granting agencies and I want to ask a couple of questions related to that. Some immediately come to mind. How did the Pew not become a more disciplinary focused grant? Why did the committee not say, "This year we want people to focus on rheumatology and next year we'll do a different focus and that way the class will have a group identity"?

WEISSMANN: Number one: it never arose, it was never discussed; it didn't get discussed because the founding group, including Josh and most of us, had M.D.s and we were broadly interested in the biomedical field. We'd say, "Gee, how about some plant science or you know." Or, "There's too much X and too much Y. Why not Z?" And I remember, the discussions I liked most were when we were getting too narrow in terms of informational macromolecules, for example, which was big at the time. They forgot everything that had to do with receptor/ligand interactions. Now, of course, it's signal transduction or oxygen chemistry, if you will. I've done a search for the key words over the years and it's—Look, abstract painting is a form. There's no subject matter and I think good science is like abstract painting. The composition is there and it just sings like a [Mark] Rothko painting. A lot of applied science however, is like a comic strip, or Bart Simpson. But good science is pure clean science. Whether it's done in population based studies on who gets melanoma and who doesn't or, on the other hand, what plant enzyme blocks RNA.

DAEMMRICH: What I'm hearing from you is that you're looking for applicants who have already made some significant discovery that has real world application that matters to patients and that they're laying out new research?

WEISSMANN: No, I disagree. Some people might look for it, but not me. I just want to know is it a "wow"? Again the best analogy is [Sergei] Diaghilev to [Vaslav] Nijinsky, *étonnez-moi*: astonish me. When you're astonished, that's it. You got it. Now I know there are people who don't work this way, but that's the way I work.

DAEMMRICH: The point being they had to have made some "wow" discovery already and then be applying for the Pew grant to get them to the next level.

WEISSMANN: Yes, because in my experience, that which people promise they're going to do is usually just speculative talk and hope. NIH grants ask you to detail exactly what you will be doing five years from now. I've applied for those and I've gotten lots of them and it's always boilerplate: you know that what has worked before is going to get funded. People say, "We fund innovative research," but they don't. Moreover, you can't tell what you're going to do in the next five years. I never got an NIH penny for doing liposomes, ever.

Again, Weissmann's homilies. [laughter] The job of the scientist is to be like a painter in Renaissance Florence: the donors want you to paint their pictures in the *predella* panel, but your job is to paint the saints or the Virgin Mary. You do what you need to do and tell any lie you need to in order to get the money to do your business. If you do only what you say you're going to do and promise to do it, man, you're going to get nowhere. But you can sense that from applications.

Also, a few imaginatively written proposals, although I usually don't look at proposals all that carefully at all, a few just grab you: "what a spectacular idea." It doesn't matter whether they'll do it or not, it's just a great idea. But it's that kind of discovery that's a pleasure. I go over ten to twelve manuscripts a day as they come in to the *FASEB* [Federation for American Societies for Experimental Biology] *Journal*. Same thing.

DAEMMRICH: In the early years, as the grant's getting off the ground, the program is creating an identity. Did you and other committee members work to promote the grant?

WEISSMANN: I didn't. I have a fairly broad network of people with whom I speak with and people asked me about the program. People asked, "Gee. Should I apply to this Pew thing?" Some people I told yes and some no. A number of my students have done that.

DAEMMRICH: If you were to try to kind of boil it down or summarize it, what kinds of things was the committee talking about in the mid-1980s?

WEISSMANN: There was a lot of discussion to begin with. A lot of it had to do with how backward we should lean for people who had mainly clinical training or what the ratio of our funding should be between Ph.D.s-M.D./Ph.D.s. Since many of us had M.D.s, we wanted to encourage people who had perhaps less of a published research track record but seemed like brilliant people. A major discussion centered upon clinical versus non-clinical research. Enough training, and we really wanted good science, but in terms of what the mix should be, I was sticking up for people like the bright chief resident who's gotten one experiment that really was a "wow."

But mostly everybody was so delighted to be on a committee that didn't have to do NIH-type of stuff. [laughter] Well, we've all done NIH stuff. You simply look at the application and you fund people through that and their C.V. Here you funded a C.V., a potention scholar's life in science, and the application was important, but not the deciding factor. Generosity to new ideas is not evident in NIH study sections and, therefore, not evident in NIH funding. At Pew you feel pretty good about what you can do. You feel pretty good about permitting others to do well without the nitpicking and so on.

DAEMMRICH: The thing that they're going to discover in the lab on their own and then switch to a different buffer or other such details may or may not be the reason to fund the grant.

WEISSMANN: Exactly. Again, the big argument: what's the discovery? What do they promise to do? If they promise to do something unbelievable, it doesn't matter. I was wildly impressed by Josh's selection, which I think got better as it's been trimmed down. It is interesting that by 1993, Pew funding had been switched significantly to a more basic science.

DAEMMRICH: While you were still on the committee in the early 1990s, the human genome project began really ramping up. Did that have any effect on the kinds of people you wanted to fund?

WEISSMANN: I got into a fight with Norton Zinder regarding the genome project. I said it's going to be a huge waste of money, the dumbest thing that ever happened. You're going to diffuse scientific integrity and so on. I was wrong. I was wrong and I've changed my mind in print. [laughter]

DAEMMRICH: Did it play out at all in the Pew group?

WEISSMANN: Not then. Right now, I'll reject genome or microchip papers that simply say, "These genes are there, they go up and these go down." I mean, that's bean counting, not

science. However, you need to know how many beans are in the world and what their names are. No argument there.

There were discussions about genome related research. The other discussions we'd have at some of these meetings—Josh is interested in the anthropic principle, which I think is a crock of shit. It's just a Panglossian view—the best of all possible worlds and the best of all possible outcomes. We know from computers and silica that you can make another kind of world. Every once in awhile a scientist, whether they like it or not, drifts into some notion of intelligent design or vitalism. As you may gather, I'm on the other side of that. I loathe theoretical biology. I love ideas, hate theories.

DAEMMRICH: Especially unified theories. In the early 1990s Josh stepped back and Torsten [N.] Wiesel stepped in as chair. Was there a change in how the committee worked? I know one thing he did was implement a formal rotation policy.

WEISSMANN: I was delighted to be off the Advisory Committee. Ten years was enough. It's more than enough. And I think that's absolutely correct. Torsten's a great man, and I think he is a bit more formal by background, training, and attitudes. Josh works on bugs, Torsten on the head. Bugs are more unpredictable than a human head. [laughter] I just think they have different styles, but they're unbelievably admirable. I still think that Josh is just one of the major giants I've ever met. He's in such terrible shape now it's a shame. I just spoke to him. One out of three days he says he's back to where he was.

DAEMMRICH: I was really fortunate when I met with him; he was completely lucid and energized and ready to go.[25]

WEISSMANN: He's an amazing man.

DAEMMRICH: I want to play devil's advocate for a minute and show you something. Here's a graph showing NIH appropriations. Look at the period in the mid-1980s when the Pew grant is starting. In the next two decades, NIH's budget doubled twice, or more than twice, in that time period. What can the Pew program really do if it's funding only twenty people a year?

WEISSMANN: Well, I happen to know the analysis for these figures. If you look at the productivity, which means paper publication, it's flat. The bulk of that money is going for huge projects by groups, translational research, log rolling, deans' overheads, and department building. This new guy, Elias A. Zerhouni—who is essentially a patented radiologist and charming—can only think of big teams and big equipment. NIH money is being thrown away right and left by people who are extremely good at organizing large grants and cooperatives and

consortia. My feeling is that without things like the Pews, the Ellisons, the Wellcome [Trust]s, we'd be locked into big science and not individuals. While there's a place for big science and I've got no problem with that—the enterprise is there and we need consortia of sorts—I'm thrilled by the individual and these smaller funding opportunities are wildly important. Also, to the degree that getting a Pew was like getting a Fulbright or a great residency—it's an *imprimatura*. It's an elite reward, but so is the *Legion d'Honneur*. There's nothing wrong with elitism to an extent. It is a system that rewards some and disappoints others. The award of a grant by the NIH is, in part, a recognition of real science, real accomplishment, but also it's always suspect in the way that affirmative action is always suspect. It can do great things, but there's always a suspicion.

DAEMMRICH: That it involved pulling strings or—

WEISSMANN: Oh, no. University, or political, or geographic issues of course.

DAEMMRICH: Well, it's government funding. It's taxpayer based and so is political by nature.

WEISSMANN: Of course. Why do you think they notify your congressmen when you get an NIH grant? If it isn't exactly pork, it ain't caviar. [laughter] I think the Pews, Ellisons, Wellcomes, these grants are caviar and a lot of NIH grants, I'd say about 40 percent, are pork.

DAEMMRICH: What sort of strings ought to be attached to the Pew funding for the scientists?

WEISSMANN: None. I think money ought to be given directly, no overhead, no categories, no nothing. I don't believe in overhead because it just means the money is wasted. I think it ought to be money given to the scientists to do whatever they want to do. I mean the university does the accounting for it. It's uninteresting. It's bookkeeping. You give the money to the institution and the institution does its accounting anyway. There was discussion about that.

DAEMMRICH: If I'm on the board of Pew Trust and you're going to report to me, "Here's why we're giving this money and to whom, and here's what it will produce." How were you doing that type of report?

WEISSMANN: I'd report it very simply. We're giving money to scientists to make discoveries. Here's the track record of these people five years later, not during their Pew tenure.

This is what they've done. This is where they are. This is a control experiment of the ones we did not give the Pew funding to. I insisted early on there be a control. It still hasn't been done.

DAEMMRICH: So they haven't been doing that level of accounting? That would be a fascinating study.

WEISSMANN: That's the study to determine if we were picking right? It doesn't mean that the money made it possible, not at all.

DAEMMRICH: What would be some of the good measures for effectiveness of the grant?

WEISSMANN: Number of citations five years out.

DAEMMRICH: How many of their articles were cited how many times?

WEISSMANN: Yes, you can get that in total citations. That's perfectly fine.

DAEMMRICH: Would it matter where they end up professionally?

WEISSMANN: No.

DAEMMRICH: Would you look at others?

WEISSMANN: The control is the applicants you didn't pick. That's all. You have a built-in control group. It's easily done and they're easy end points to get. For example, I evaluate what I do in the *FASEB Journal* every month: how many hits do we get, how many citations? We've run it like this since I took over and I'm thrilled. We've got a curve like this [hand gesture] in terms of submissions. And now we'll see what the citations are. But I believe in this kind of quantification. There are ways of quantifying scientific discovery and Josh is very good at this.

DAEMMRICH: How are the universities that can nominate a Pew scholar selected?

WEISSMANN: NIH funding. Top forty or so. It should be. That's the appropriate environment, whether it be political expertise or not, but that's the environment. Scripps [Research Institute] gets more money than the MBL [Marine Biological Laboratory at Woods Hole]. Scripps is higher on the list than the MBL. So perfect, no problem.

DAEMMRICH: Tell me, reflecting back on the decade you were on the Advisory Committee and now, almost a decade's distance—

WEISSMANN: And the funny thing is Josh and I have been doing it now for the Ellison, so it's a very similar. I've been doing this for twenty years; it's very similar.

DAEMMRICH: You drew on the Pew experience, then, in helping structure the Ellison?

WEISSMANN: Yes, completely. There wouldn't have been an Ellison if there weren't a Pew.

DAEMMRICH: Looking back, what would you say that Pew ought to change about the Advisory Committee and about the grant?

WEISSMANN: I think they have a superb bunch of people looking at it. They've got some great fellows. They've got good results. The five-year follow-up, in terms of awards and so on, has not been terrible. The two people I know closest who worked with me who got Pews are both full professors at Harvard and they weren't when they started. A lot of the people I've gotten to know in science I first got to know as Pew fellows. Jeffery Ravetch is a Pew scholar who I pushed for because he's working in immunoglobulin receptor research and I thought it was important because that's the receptor that permits liposomes to enter a cell.

By and large the track record has been impressive and I would not switch anything. If anything, whatever restraints, or problems, or directions there are, there should be fewer. Whatever directions or paper there is, if you cut it by at least 60 percent, it would not hurt anything.

DAEMMRICH: Right. That's a good general rule of life. [laughter] Is there anything else looking back that you would want to say about the Pew program and or being on the Advisory Committee?

WEISSMANN: Well, I think the business of having meetings in resorts in Mexico is dumb because it's a drag to get to. You don't learn foreign culture. Instead, you learn foreign resort

culture. And number two, I like the idea of retreats, but it's a bit artificial, that's all. It's not terrible. It's lovely. They're a good time. I don't go for South American retreats. If you really want to do it, go to the south of France. [laughter] No, but that's a fine culture.

I'm joshing. Some of those meetings are spectacular. You learn a lot sitting around a pool, standing half in the water, and getting sun burned. Mike Oldstone of the Scripps [Research Institute] and I had a discussion on how viruses ought to work and I still remember it to this day.

Also, point of honor. In Cozumel[, Mexico], Lubert Stryer and I had a discussion over cocktails about what is the definition of a gene. It is actually very tough, you know, genes begin as a promoter region, but transcriptosome assembly and redundancy dictate all kinds of structure. When exactly in the nucleus does a gene begin? Well, we started with the definition of Otto Loewi, here at the MBL, years ago. He said, "a drug is a substance which when injected into an animal produces a paper." [laughter] We came up with a saying that I frequently show as a slide: "The Cozumel definition of a gene, Stryer and Weissmann." I forget the year: "A gene is a substance which when deleted in a mouse produced a paper." You talk about what happens at meetings, that's what happened at one meeting. I've again withdrawn my opening statement about them being a dumb idea. If it had been in some other place, we probably wouldn't been—

DAEMMRICH: Without the meetings, there wouldn't have been that degree of both science and a little light-heartedness.

WEISSMANN: Exactly—after a couple of margaritas. [laughter]

DAEMMRICH: I looked at a couple of abstracts of your current research—

WEISSMANN: I stopped doing experimental science about three or four years ago. I devote myself entirely to literary work and running a biotech[nology] center.

DAEMMRICH: Well then, the experimental work from right before you stopped was on leukocyte activation.

WEISSMANN: Oh yes, that's from 1970 onwards. Everything has been directed to working out how neutrophils release their inflammatory products: either superoxide anion, prostaglandin related material, or lysosomal enzymes and that single transduction membrane interactions where the downstream molecules are factors. So we traced it down to the MAP kinases erk, erk2: aspirin in high doses interfere with that. In macrophage and other cells, cortisone

interferes at the nuclear level with the inhibitors of that transcription process. So we followed it all the way down to the gene level. This is where steroids work and non-steroidal anti-inflammatories work higher up in the cascade of signal transduction from the outside to inside. Corticoids work on transcription down here. So that's it in a nutshell.

DAEMMRICH: That was quite the nutshell.

WEISSMANN: Basically, a narrative description of what I've been doing is: outlining mechanisms of inflammation caused either by endogenous or exogenous agents and how agents that we know work, work. Since we reduced inflammation to the neutrophil, we reasoned that if you can understand it, you can begin to generalize to the other cells of inflammation. They're just cells and so it works out relatively the same. There are similarities, of course to more complicated cells, like macrophages or dendritic cells, but those neutrophils have microtubules, microfilaments, actanin, open membranes, receptors, signal transduction, and all of the signal transducing molecules. And by sticking to one cell type that you know well, you can generalize. That's it.

DAEMMRICH: Well, it's fascinating. I want to shift now to talk a little about some of your more popular writings. I've really enjoyed reading some of these. Of course, given my academic background, I especially enjoyed reading the piece on Ludwig Fleck because, in many ways, he is the not-properly-recognized founder of the sociology of science and the sociology of scientific knowledge.[26] People always turn to [Thomas S.] Kuhn.

WEISSMANN: Okay, sociology of science. One of the things I did at NYU when Wassily [W.] Leontief, the Nobel Prize winning economist, retired from Harvard, he and I, together with Dick [Richard] Sennett, a sociologist, put together a society of fellows where we met in the evenings to talk. After the gathering of one of these, Kuhn and Sennett and I started discussing Fleck. Tom was just getting a divorce, I think, and was moving to New York and we had this discussion of who really started the sociology of science. And I'll tell you exactly who it was and it wasn't him.

Have you ever heard of [Wilfred Trotter's] *Herd Instinct*? Sociology of science started a bit before Fleck. It was really an English innovation. Fleck didn't know any of this. But Fleck's model of the soccer game, as the model for doing science, the dynamic aspect, was something very Central European. Think of [Sigmund] Freud's dynamic unconscious. So what Ludwig Fleck was doing, essentially, was to elaborate a dynamic unconscious of science.

DAEMMRICH: The concept of a *Denkkollectiv*: a collective thinking on a topic.

WEISSMANN: The ideas of Sigmund Freud are part of the Central European *Gemisch* [medley] and that is the matrix from which both came. And you know why? Fleck and Freud were Jewish in the Catholic society of Vienna. The *Denkkollectiv* was Fleck's experience in that westernized, European Jewish group that knew there were collective forces underneath all that hierarchy of state order. They were groping for that as a general phenomenon. Everybody feels that they're part of some, if you will, Invisible College. Now, the sociology of science was also first spelled out by Thomas Sprat in his *History of the Royal Society* from 1667.[27] It's spectacular. Anyway, I'm not uninterested as you may gather.

DAEMMRICH: This is really enjoyable. One of the things I've been struck by in some of your more recent pieces, especially in *Darwin's Audubon* and also just looking at the title of your most recent book [*Galileo's Gout: Science in an Age of Endarkenment*], is that you're articulating a concern about the perception of science.[28] In particular you see a divergence between how the public views science, technology, and medicine and how scientists see it.

WEISSMANN: Completely. I think that it is a time of "endarkenment." The 1960s, which had a terrifically good influence opening up the world to many people, had the downside of dumbing us down. And there's a great scene in the film *La Chinoise* by Jean-Luc Godard in which he has this young enthusiastic Maoist woman excited about burning down the bourgeois society.[29] An elderly professor asks, "What are you going to do when the new world comes about?" She says, "Well, we'll go read and study." And he says, "Well, where will you read and study after they burn all the libraries?"

I think we've come to a point I hope is a transitory stage in history: changing the world by reason and science. We've had that world since Francis Bacon's *Great Instauration* of 1620 and it is beginning to fall apart to a large degree because of mystical and religious beliefs.[30] I am a big fan of [John] William Draper's 1874 book *History of the Conflict between Science and Religion*.[31] I think there is constant warfare and it is not reconcilable. One is magical, the other is not. Moses did not come down from the temple nor did Christ walk on water, and if you believe they did, you're crazy. So, I'm a reductionist. You can't have this world and that world at the same time. If you think they can coexist then, like Francis [S.] Collins [of the Human Genome Project], you've got a problem. And you may also have someone in your lab who fudged. You know that story. Francis Collins is one of the people I've written about in one of my editorials, "From the Patchwork Mouse to Patchwork Data," about recent frauds.[32] One of the biggest ones came from Collins' lab.

DAEMMRICH: I was at a Pew meeting earlier this spring where Collins was giving a talk and one of the people in the audience said to him, "So, instead of saying the earth and everything in it was created four thousand years ago, which you oppose, you're saying there was this moment when a deity created a set of circumstances that would lead to everything else. So what you've done is push the clock back chronologically but have you done anything else?" That produced an interesting dialogue.

WEISSMANN: The views I've just expressed are not those I have intended for immortality, but I have the prejudice of my background, class, and training. I think that people who believe in God are just slightly dumber than those who don't. It's a belief. Their belief may be the opposite. But I think it is an era of dumbing down and this has now reached massive proportions.

DAEMMRICH: Part of your purpose in writing is to analyze the situation and also bring about some change.

WEISSMANN: I don't think that anything I write will change anyone's mind. It may reassure those who think as I do. I don't have that larger readership—if these things sell ten or twelve thousand copies, I'm lucky. The journal reaches a lot more and so do my editorials. When I was editing *MD Magazine*, I reached a hundred thousand people, but I'm not a [Jerome] Groopman. If you look at the bibliography of the "popular" writers on medicine and science, and you'll see they're working in the present tense. I use the past as a lesson.

DAEMMRICH: Yeah.

WEISSMANN: And it's the same argument that we had about the Pew. I'm trying to support an elite structure to work in.

DAEMMRICH: Coming back to this notion of an age of "endarkenment," I understand your point about how it may have come into being through opening up and challenging power structures in the 1960s and 1970s.

WEISSMANN: Look, after God failed, there was no good secular alternative that could enthuse a crowd other than totalitarianism (Nazism and Stalinism). So given that example, you could see why a lot of people turn away from it, especially for the bulk of the world that hasn't gone through their enlightenment. They had no model.

DAEMMRICH: There is another piece of this I wanted to explore with you, that I think is really interesting, and you may see them as part of the whole, is that there are many people today who are identifying ailments that they have, or they believe they have, through the internet. Subsequently, they form communities around disorders that hard-line scientists say there's no molecular basis for and, therefore, are not diseases. I am thinking of things like fibromyalgia.

WEISSMANN: I've become a point of attack by the Chronic Lyme people already.[33] And, not to forget total food allergy, restless leg syndrome—*Saturday Night Live* did a great parody of that: restless penis syndrome; I loved that—that's how I feel about fibromyalgia, chronic fatigue syndrome, and similar ailments. By definition if you have one, real, measurable, metabolic abnormality, you have another diagnosis. If you really have something wrong with you, you can't have fibromyalgia. You just have to have pain to carry the diagnosis of fibromyalgia. If your sed[imentation] rate is up or you have an enzyme that is elevated, you don't have the "condition." People die of diseases, they don't just have conditions. Even schizophrenics commit suicide.

But, have you seen the play adapted from [Aldous] Huxley's (1953) *The Devils of Loudun*?[34] It is about mass hysteria and the delusions of crowds. It's understandable. I mean it happens. Look, people like Günter Grass joined the Waffen-SS with a jolt of group identity. Platoons of ladies who swig plastic bottles of water all day join fibromyalgia support groups. It's the same thing. One's aggressive, the other passive. Both are irrational, unreasoning. It's amazing how aggressive some of the passives can be, by the way.

DAEMMRICH: The idea of community building around disease is intriguing.

WEISSMANN: The man who has done that very nicely is Edward Shorter. I love his work. I'm really a big fan. By the way, it's also true about real disease. One reason that an intravenous drug used to treat lupus is very helpful for patients is because they're in a transfusion community where they all get their IVs at the same time. It's like hairdressing; and I don't say that to belittle it at all. But it does create a community. People willingly share their symptoms.

DAEMMRICH: And then they could share in the healing.

WEISSMANN: By the way, no physician worth his salt uses the word healing. It's a spiritual word.

DAEMMRICH: But if it's a community based activity more than a molecular one, then maybe it's—

WEISSMANN: Well, that may be, and I'm sure it engenders some sort of molecular arrangement by definition, but I've written about this for so long that I'm bored with the discussion. Diseases tend to hurt you and you can die from them. There are drugs that can fix

it. Diseases that are of the mind are also very serious to those who suffer from them and no one's arguing. It's the medicalization and the attempt to turn this into a physiological condition starting at the external level rather than internal level is what I'm complaining about. These people are sick and I feel wildly sorry for them. I mean, my God, you've got a disease that you can't name, you can't do anything about, you're in pain, but you can then say, "Oh, it hurts all over." Good, then you have a fibromyalgia support group. That's probably all right.

At least you're not burning the Chronic Lyme Disease people at the stake, which people who believe in religion—which is, in other ways, a disease. Look at the three major diseases of humankind: Muhammadism, Christianity, and Judaism, all of which started in the Middle East and all of which have killed more people than any disease that pharmaceuticals ever tried to help. The fibromyalgics aren't doing that. So if you want to call that a religion, they should have it and be well. [laughter]

DAEMMRICH: How do we better communicate science to those kinds of audiences? How do we involve the public more in science? I mean is it okay that it remains elite?

WEISSMANN: Let's put it this way. I know very few Swedes, Scandinavians, Scots, or a good bunch of Frenchmen who have the same kind of fuzzy ideas of science that many Americans are permitted to have. They send fewer of their people to college. Our college graduates think they're educated. But, you don't learn about science or think about science if you major in sports management at Ohio State [University]. How do we involve the public? Number one, tighten up education. We can't do that as scientists. I can't substitute for that. And number two, there are other agendas in our society that are much more important to our well being at the moment than the public knowing about science. Maybe we should learn about social democracy first.

DAEMMRICH: Right.

WEISSMANN: Years ago, I was invited to give a lecture at the Asian Conference in Rheumatology in Bangkok[, Thailand]. The man in charge arranged a press conference just as we got off the airplane. He introduced us and said, "These are the people who'll be interviewing you and we'll continue the press conference at the hotel." There was a lot of noise and traffic to pass through as we were then driven through Bangkok and we get to this unbelievable place, the Mandarin Hotel. He said, "Tell me, what do you think the most important thing about treating lupus in this country?" I said, "Well, I think public health is probably a more important issue right now," because basic sanitation was still an issue.

Likewise I'm going to argue that in America right now, the most important thing is not for Americans to learn more about science, but—and this is said with great respect for the Pew

Foundation with its interest in support of religion—but to learn again the lessons of secular humanism, which has produced modern science.

DAEMMRICH: Good. What did I miss asking you about?

WEISSMANN: I think you got it all.

DAEMMRICH: This was fabulous. I mean we could go for hours. Thanks so much. It was really enjoyable.

[END OF AUDIO, FILE 1]

[END OF INTERVIEW]

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