National Institutes of Health
Interview with Dr. Julius Axelrod
Conducted on November 25, 2003,
by Dr. Marshall Nirenberg and Dr. Bernhard Witkop

Introduction: This is an oral history interview sponsored by the Office of NIH History on November 25, with Dr. Julius Axelrod (JA), now an emeritus scientist at the National Institutes of Health and formerly the Chief of the Section on Pharmacology in the National Institute of Mental Health. Dr. Axelrod won the 1970 Nobel Prize in Physiology or Medicine for his work on neurotransmitters. The interviewers are Dr. Marshall Nirenberg (MN), Chief of the Laboratory of Biochemical Genetics in the National Heart, Lung, and Blood Institute and also an intramural Nobel laureate, and Dr. Bernhard Witkop (BW), now an institute scholar and formerly the Chief of the Laboratory of Chemistry in the National Institute of Diabetes, Digestive and Kidney Disease.

MN: Julie, tell us about your parents and early upbringing.

JA: Well, my parents came to America from Eastern Europe around the beginning of this century. It was a great immigration of many Jews, called the Goldina Medina, the Golden Heaven, and they met here, they settled on the Lower East Side of New York. That was where most of the Jewish immigrants came and settled, on the Lower East Side. They met, and they came from a similar area in Eastern Poland, Galicia. They met here and married. And I was born in a tenement–in the fifth floor of a tenement on the Lower East Side, on East Houston Street, and my upbringing was very typical of immigrant

Jews. I went to *haida*, as well as the public school, and I went to an elementary school which was built during the Civil War. It was very old, and one of the very distinguished graduates of this public school was Isidor Rabi (1898-1988).

Well, my life was mainly on the streets of the Lower East Side. We used to play all kinds of games, such as stick ball. I learned how to swim by jumping into the East River, which was very close to where I lived. I went to a junior high school, Mangin Junior High School, and when I graduated, I wanted to go to Stuyvesant High School. That was a high school, a very elitist high school for the very bright kids, but I wasn't good enough to get in, and I went to a school called the Seward Park High School. It was opposite, I remember, the Forward Building, that was the Yiddish newspaper at that time, and many of the graduates were very well-known entertainers, Zero Mostel, Tony Curtis—his name was Bernard Schwartz then—Walter Matthau.

You know, every dream of a Jewish mother is to have a son who is a doctor, and this was my goal, you know. I was very much influenced by my mother. She was a very wonderful lady, sweet. And when I graduated from high school, I saved up some money, and I was accepted by New York University. At that time, New York University had two parts; one on Greenwich Village, Washington Square, and one uptown. It was sort of a campus. I wanted to go to the uptown campus, because it was very much like, a lot like, a real college campus. I was interviewed by Admissions, and he asked me where I lived.

I said I lived on East Houston [pronounced Howston] Street. "Oh," he said, "you mean Houston [pronounced Hyooston]," and I knew I wasn't going to be accepted.
I was accepted, though, at the Washington Square annex of New York University. The reason I went to New York University, I thought it would give me a better chance to get into medical school. After a year, my money ran out, and I applied to City College. City College at that time was a tuition-free school, and it really had a Gothic campus, although it was in Harlem. I remember going from the tenements, the Lower East Side tenements, by subway to this Gothic campus, City College. It was really, I think, one of the most important influences in my life, going to City College. Most of the students were very bright and highly motivated, highly political. This was in 1930. It was the beginning of the Great Depression. As a premed, I majored in biology and chemistry, although my subjects I was most interested in were history and philosophy and literature.

I didn't do too badly in all of these courses, and I had some really wonderful professors. One of the professors was a very distinguished philosopher, Morris Rafael Cohen, and I was very much interested in philosophy. At City College there was a lot of turbulence at that time, you know, because of the rise of Hitler and anti-Semitism and fascism in Italy, Mussolini. City College, in a basement [of the main building] called Shepherd Hall, had various alcoves. Each alcove had a group of students which had different political ideas, and there were very many heated discussions amongst them. There were Trotskyites, the Stalinists, the Socialists. There were some fascist Italians there. I was just fascinated by this type of environment.

I graduated, and when I graduated, I applied to several medical schools. I wasn't accepted by any. I was very lucky; I heard that there were positions called volunteers, and I was interviewed by a very eminent biologist, William H. Park (1863-1939). He was the one who introduced diphtheria vaccine in this country. He suggested that I see a biochemist who had a laboratory at New York University Medical School. That was located then, and still is, on Thirtieth Street at First Avenue. I forget the name of the area.

K.G. Falk was the man who hired me. I was paid twenty-five dollars a month, but I was very, very glad to work in a laboratory. At the same time, I took an examination for a clerk in a post office. I was accepted, but I decided to work in a laboratory. You know, I had many decisions to make in my life, and, looking back, I made all the right ones, choosing the laboratory, although I could have gotten much more money working in the post office. Falk was working on enzymes in malignant tumors. He was supported by Harriman. It was called the Harriman Research Institute, which was located at New York University, and I assisted him in working on enzymes, esterhydrolyzing enzymes in malignant tumors.

Falk wrote a book in 1924. He studied biochemistry in Europe. He was very much influenced by a very famous biochemist, Richard Willstatter (1872-1942), who believed enzymes were just catalysts which were adsorbed on proteins. He believed it till the day

he died, even after J.B. Sumner (1887-1955, Nobel Prize 1946) crystallized urease. Well, anyway, it was an interesting job. It was not great research, but I had a little taste of research. I worked there for two years, and I decided to get married. I met a lovely lady, Sally Taub, who ultimately became a schoolteacher. I knew I couldn't get married on $25 a month. Even in those times, $25 a month wasn't very much.

Fortunately, vitamins were then discovered and introduced and used as supplements. They were added to milk and pills and things. The City of New York set up a laboratory to establish whether the supplements, the vitamin supplements that they added to milk and things, were what they said on the label. And they set up a laboratory to see, and I was hired. It was called the Laboratory of Industrial Hygiene. I was hired, and I was given a good enough salary to get married. The experience I got at this laboratory was to test vitamins in foods, and this involved reading the literature and applying the methods that were published in the literature of foods, and it was very good experience for me. They also had the *Journal of Biological Chemistry*, which I used to read, and I became very much interested in the developments in those days. One interesting development was the discovery of dicoumarol. I happen to know the man who made this discovery. It was Karl Link.

BW: Karl Paul Link (1901-1978).

JA: Right. He looked like a Shakespearean actor. He had a cape and a black broad-rimmed hat. I followed the story. Cows were dying of sweet clover disease, and they bled to death. Link was a professor at Madison, Wisconsin, and I happened to read each installment of the isolation of the active principle, while I was working at the Laboratory of Industrial Hygiene, on the vitamin. He isolated the active principle of sweet clover disease, dicoumarol. He went to the clinicians at Wisconsin and suggested perhaps it would be a good anticoagulant. They looked him up and down. "You're just a farmer," they said. "You'll kill people," they said. "It's rat poison."

However, there were very astute clinicians at the Mayo Clinic, which wasn't very far, and they introduced—well, this is one of the side issues. I used to read the *Journal of Biological Chemistry* regularly, and I became very much interested in research, although I was doing this fairly routine thing, although it involved some type of ingenuity, you know, to apply a method, say Vitamin A, to test it in foods. Also they had assays, bioassays, for Vitamin D, for example. What we did is, we used a diet which was free of Vitamin D, and the rats came down with rickets. How we tested it, we'd take the bone and use a silver stain, etc. I remember, while I was working, I had to make up the diets for these. I used to go to the Fleishman Yeast laboratories in the Bronx. I always liked going there, because it was opposite Yankee Stadium, and I took the opportunity to go to the ball game while I was there.

The experience, at least in retrospect, was very useful. I'll get to how I got into research in a minute. The head of the laboratory was a very distinguished pharmacologist, George B. Wallace, who was a former professor, head of the Department of Pharmacology at New York University, and he actually was the editor of the *Journal of Pharmacology and Experimental Therapeutics*. One day a group of manufacturers of analgesics, called the Institute of the Study of Analgesic Drugs, came to Wallace with a problem, because some of the non-aspirin analgesics used in those days were acetanilide and phenacetin, and one of the problems was that some people became habituated to these. They had them in Alka Seltzer, whatever, and some of them came down with methemoglobinemia. They were very concerned and wanted to know why.

They came to Wallace for advice, and Wallace asked me if I would like to work on this problem. I said, "I have never had any research experience." "Well, I suggest you see a colleague of mine, a former colleague, Bernard Brodie." Do you want me to go on, or do you have another . . .

MN: Sure. This is exciting.

JA: [Laughs] I was asked to talk. Well, I went to see Brodie, Dr. Brodie, in his office. At that time, it was Goldwater Memorial Hospital, which was on one of the islands on the East River.

BW: Welfare Island, yes.

JA: You know Goldwater. We'll come to that. I went to visit him. I remember the day. It was February 12th. It was Columbus Day, I think, in 1946—to discuss this problem with him, and he told me something which I vaguely was aware of. He told me that anytime one takes any kind of a chemical, a drug, it's transformed in the body. One thing I learned from Brodie is to ask the right questions, and he asked me to put the structure of acetanilide on the board, on his blackboard, and he looked at it for a while. I don't know whether you can visualize acetylanilide. It's a benzene ring having an amino group which was acetylated, and one of the transformation products could be a de-acetylation to aniline.

I looked up the literature and saw that an aniline could cause methemoglobinemia. If you ask the right question, you have to go about learning how to answer these questions. The next thing, I developed a method—one thing I was good at it—developed a method to measure aniline, and how it was done is to diazotization and couple it to a dye so it would have a color. I developed a method, with Brodie's help, a very sensitive one. I took some acetylanilide—I found some aniline in my urine, and this, of course, was one of the most exhilarating experiences—you would know this, Marshall—when you make an important discovery for the first time.

MN: It's exciting.

JA: There's nothing like it. And we found that if we give aniline to dogs, it causes methemoglobinemia.

BW: And what about the metabolite? You found the metabolite.

JA: Oh, yes. That was even more important. [Laughs] I don't know. You have so many other questions, but starting with your first question . . .

BW: You were on the threshold of becoming a millionaire.

JA: Well, at that time, I was working for a University and couldn't patent things. But anyway, the aniline represented only 4 percent of the ingested acetanilide, and that was completely metabolized, in a rabbit, anyway. So we wondered—Brodie and I interacted. He was a very stimulating, charismatic man, and he really fired you up, you know. We suspected that one of the metabolites would result from a hydroxylation on a para-position. We developed a method for it, and we found it was in the urine and most of the blood, N-acetyl-para-amino phenol. We had it tested for its analgesic activity. It was analgesic, just as good as the original parent compound, and it represented about 80 percent of the metabolites, and it was nontoxic.

When we published our first paper, we said that should be considered as a safe analgesic. It doesn't cause methemoglobinemia. And it's what is known today as Tylenol. Actually, if you write "N-acetyl-para-amino phenol," Tylenol is encrypted in that. The same thing, acetaminophen is also. Anyway, that was my first experience in research. I loved it, and I thought, "This is what I wanted to do for the rest of my life."

MN: That's terrific.

JA: And, you know, Goldwater was a very unusual place. I was struck lucky, you know. I'd like to digress, give a little background about Goldwater. During the war, the Japanese cut off the supply of quinine, and the troops were fighting in the Pacific, and they needed desperately an anti-malarial. So they set up a unit at Goldwater headed by James Shannon (1904-1994). James Shannon was a professor of physiology at NYU, worked on the kidney secretions, etc., but he happened to be, ultimately, one of the great scientific leaders, you know, administrators. Well, he was the head of that program to test drug levels, to test whether synthetic drugs were anti-malarial drugs. It was a very stimulating atmosphere that I was thrown into. Although it was after the war, they continued working, and they had some very, very bright people there. Many of them came here to the NIH. There was Robert Berliner (1915-2002).

MN: Berliner was there?

JA: There was Zubrod in cancer. There was Bowman, Bob Bowman; Sid Udenfriend; Herb Weissbach. Well, anyway, let's go on. If you have any other questions we can—that's my beginning.

BW: Yes. You're attaching the memories. You know, we both arrived at the same time, in 1950. You came from Goldwater. We came from Harvard. We were a small minority of only four or five people, among them, the later Nobel Laureate Chris Anfinsen (1916-1995) and Earl Stadtman, of course. And then when we met for the first time, I think you were part of the retinue of Sidney Udenfriend (1918-1999), and immediately you sent out good vibes. I wrote recently, with your help, the biographical memoir of Sidney Udenfriend, who died four years ago as the director of the Roche Institute of Molecular Biology, one of the few cases where somebody left the "NIH rest home" to go into the cruel world in order to compete, and he did very well. And I think you will remember the stimuli that you got from Udenfriend.

I may go back to what Vicky Harden said. She said the first Paul Ehrlich Lecture, which was established in 1988, when I retired, demonstrated quite clearly how scientific ideas are connected over time and how an understanding of what has gone before may lead to fruitful new research. I think the environment and the closeness of Udenfriend, his interest in serotonin, guided your research into many directions, so that you laid the fundament for the treatment of depression. Can you tell us about it?

JA: Yes. Well, I'll come to that later. That comes later, but let me continue this story. I'd like to do it chronologically, because it's an interesting story. I just had a bachelor's degree. Brodie had his lab. Shannon persuaded Brodie to come to the NIH. At that time, Congress had established the various institutes, you know, Mental Health and the Heart Institute, Arthritis, etc., and I was in the Heart Institute. The Heart Institute was located in Building Three, and also the Arthritis Institute. That Building Three was really one of the great—it's a small building, three-story building, but it's one of the most fertile grounds for research.

In that building, there were five future Nobel Laureates. There was Chris Anfinsen; (Nobel Prize 1972) there was Arthur Kornberg (Nobel Prize 1959); and there was Stan Prusiner (Nobel Prize 1997), who was a postdoc with Earl Stadtman; and Michael Brown (Nobel Prize 1985). Chris was a postdoc also. All from that one building. Imagine. More than half of them became members of the National Academy. It was a terrific—I don't know whether you remember this building, Building Three.

MN: Oh, I remember it. Absolutely.

JA: Yes. Also, Leon Heppel was there. Well, anyway, and that was the building I was assigned to, and there was nothing like being around such great scientists, future scientists. You know, it was a wonderful experience for me. And we all worked freely–

we knew what we were doing. We exchanged ideas. It was nothing like today, you know. It's such an enormous institution.

BW: Did you join Shannon's poker club?

JA: Oh, yes. Well, yes. That was Udenfriend's. It was called "Applied Statistics." We had put up a notice that on Friday we were going to have a meeting of "Applied Statistics." That was the poker club. You know, we used to play poker. [Laughter] Anyway, I remember Shirley Udenfriend used to have a special table for it.

MN: Tell me about your studies on ephedrine, caffeine, and amphetamine.

JA: Yes. When I was working for Brodie, I was working in a big team, and I didn't like it, and I was offered a job, I think, with Smith Kline. I told him I'd got it, and he says, "Well, what will it do for you to stay?" I say, "Well, I want independence." He said, "Okay." And so one of the problems, I became very much interested in a group of compounds called sympathomimetic amines. These compounds were synthesized in 1912 by Barger and Dale. I don't know whether you know Sir Henry Dale (1875-1968, Nobel Prize 1936). He was a famous British pharmacologist in 1912.

Brodie's lab concentrated on metabolism of drugs, and that was one of the things I became pretty good at. One of the drugs I was very much interested in was ephedrine.

Ephedrine had an interesting history. It was part of the Chinese pharmacopeia. It was used for 5,000 years. It was called, the active ingredient, Ma Huang. In the 1930s, it was Schmidt and Chen—I think it's Chen—isolated the active principal and showed the structure of ephedrine. It was ephedrine. And they found that if you give it to humans, it elevates blood pressure. Now there are big problems about it. But anyway, I worked on the metabolism of ephedrine. I felt it was metabolized by various hydroxylations, demethylation, methylation, conjugation and also amphetamine.

Amphetamine was actually introduced by Gordon Alles. I forget where he was. And, of course, it was a stimulant. Students used it a lot, you know, and truck drivers who want to stay awake. And also one of the interesting effects of amphetamine was that if you give enough of it, it'll cause the symptoms of paranoia, almost like schizophrenia. And I was very much interested in these drugs. Another drug I studied was caffeine. They knew nothing about the metabolism of caffeine. It was the most widely used drug, you know. I studied that.

This became the kind of work I did. This was in the early 1950s. One thing that struck me is that why are these drugs, which the body has never seen, transformed, changed, by different routes? For example, amphetamine is hydroxylated. Ephedrine was demethylated, etcetera. Like many other biochemists and pharmacologists, I became very much interested in how the body could do this. Fortunately, I had, who shared my laboratory, a postdoc named Gordy Tompkins. He was brilliant, and he kept me in stitches. He was funny. He was a wonderful guy.

MN: Charismatic. Charismatic. Funny person, yes.

JA: Actually influenced you a lot, didn't he?

MN: He certainly did. He gave me my first job, actually.

JA: He did?

MN: Yes. But go ahead.

JA: Well, you know the kind of guy he is. [Laughs] I discussed it with him. He says, "Why don't you find out what enzyme..." I said, "Well, I never had any experience in enzymology." He says, "Well," he says, "all you'll need is a liver and a razor blade and some Krebs Ringer's solution. You have a method for amphetamine?" I said, "Yes," "Okay. Become an enzymologist. It was a very daring, bold idea, to find why the body can metabolize these drugs, because a lot of people have tried for a hundred years. Well, anyway, it was just as well I was so naïve, the kind of experiments I did.

Well, the first thing I did was use a liver slice—it was a rabbit—and added amphetamine. It was completely metabolized. And I found that what happened was it was deaminated, and it wasn't the monoamine oxidase that did it; it was a totally new enzyme. Of course,

I became very much taken with enzymology, though. And at that time it was Schneider and Hogeboom, I think, devised methods for separating the various subcellular fractions by using isotonic sucrose, and differential centrifugation. You remember that, definitely.

BW: Yes.

JA: Well, anyway, I wanted to find out in which subcellular fraction this was taking place, and when I separated mitochondria, the [homogenized] endoplasmic retuculum particulates which we call the microsomes, and the cytosol. When I added amphetamine, none of them [the subcellular fractions] metabolized it. But when I added a cytosol together with the microsomes and added all kinds of co-factors, it was metabolized. And I found that it was TPN, and the microsomes and the cytosol that can metabolize amphetamine. And so the problem was, where was the enzyme located, the cytosol or the microsome? One is supplying something to the other.

So what I did was heat it to 55 degrees. When I heated the cytosol to 55 degrees and added the microsome and TPN, it worked; it deaminated. [amphetamine]. But when I heated the microsomes and added the cytosol, it didn't anymore. So I knew the enzyme was in the microsomes. And what is the cytosol doing, and what is the TPN doing? Well, one thing about Building Three, you knew what everybody else was doing. And I went to Bernard Horecker, who was working on a pentose phosphate pathway, and that required TPN. I asked him if he'd give me some of the substrates for that, and he gave

me three. I think it was phosphogluconate and isocitrlic acid, and glucose-6-phosphate. But when I added—one thing, I was a little sloppy. I didn't wash the microsome, so there was a little cytosol and when I added it to the microsomes, added it to the washed microsomes, it deaminated amphetamine. And the common thing about these three substrates is that TPN was reduced, it also required oxygen.

I also found the enzyme that demethylated ephedrine. When I added ephedrine to the same system, it reduced TPN and microsomes, it was demethylated, so I knew that it was a new enzyme. And, actually, I remember there was no such thing as Sigma then, where you could buy it. You had to make the TPNH yourself. And Gordy Tompkins helped me make the TPNH–you know, reducing it. And then, there it was. Well, there's one thing. Brodie was very upset I didn't tell him about this, why I didn't tell him, because I know if I told him it was his problem. But I don't want to go into that. But anyway . . .

MN: You were working on your own, though?

JA: Sure. Yes.

BW: Under the wings of Brodie. [Laughs]

JA: But I didn't tell him what I was doing, because I knew if I did, it wouldn't be my problem anymore. But anyway, well, this was, I think, one of the best things I've ever done. Now

it is called the cytochrome p450 enzyme. It's a big thing, you know. It's just that, you know, I did it on my own. I was the solo author, and I realized that I really could work on my own.

MN: But wasn't the next step norepinephrine, how that is metabolized?

JA: Oh, that's later. Yes. Well, anyway, I want the next question.

MN: Well, I mean, you discovered the system, the microsomal drug metabolizing enzymes.

JA: Yes. Well, this is how I did it.

BW: That's fantastic.

JA: Of course, I'm not giving you the impression that every experiment I did worked, you know. Most experiments, you know, don't work. You have to try one thing and another. But you don't want to hear all that, boring failed experiments. But anyway . . .

MN: What compelled you to get a Ph.D.?

JA: I can tell you what compelled me. I asked for a promotion. I was a GS-11 then. I discovered this group of enzymes, the metabolism of all of this. I thought I deserved it.

But, you know, the bureaucracy said if you didn't have a Ph.D.—you can't get a GS-12 without a Ph.D. Well, anyway, I said, "To hell with that. I'm going to leave." I happened to know a professor George Mandel at G.W. [George Washington University]. I asked him if I could take a Ph.D. I got a master's while I worked in New York, in chemistry. Well, fortunately, in order to get a Ph.D. at G.W., you have to take certain required courses which I already took for my master's. You have to take five exams, all-day exams, and write a dissertation.

He says, "As far as the dissertation, you can use—." I told him about the microsomal enzymes, so I didn't have to really—I'd published twenty-five papers already at that time. "And take those exams," which I did. They were really tough. And I got a Ph.D. I became very much interested in working with amphetamine, with drugs that affect the mind. I applied to the Mental Health Institute, and Seymour Kety (1915-2000) interviewed me. Evidently, I really wanted to work with Giulio Cantoni. Fortunately, Kety advised me, "No, you'd better work with somebody else."

Anyway, Ed Evarts (1926-1985) came over to my lab. He knew my work on amphetamines, and he knew I was looking for a position. He was at Mental Health–I sent my CV around. He said, "How would you like to work in my lab?" He was the head of the lab of clinical science. I said, "I'd love to." He was such a wonderful person. He let me alone. He said, "You don't have to work on schizophrenia. Do whatever you want, as long as it's novel and important." He gave me complete freedom to work, and this is how

I came to the NIMH in 1955. It was wonderful. I was glad I changed, and I'm glad I changed the direction of my research. I became very much interested in the chemistry of psychoactive drugs.

The first problem I worked on was the metabolism of LSD, and LSD, at that time in psychiatry was very fashionable. They thought this would give you the clue to schizophrenia, but LSD has—a very astute nurse, psychiatric nurse, can tell the difference between anybody who took LSD and amphetamine, because LSD doesn't resemble schizophrenia at all, but amphetamine does. But anyway, they were very much interested in LSD and so we worked on the metabolism, and I collaborated. First, developed a method. Bob Bowman, who used to work at Goldwater, was then building a model fluorophotometer, spectrophotometer. It was a collaboration with Sid Udenfriend, and I used his experimental models, which ultimately became the Aminco-Bowman, which was very important in neurotransmitter research for serotonin.

BW: It's in the Stetten Museum, you know, a classical instrument. DeWitt Stetten, Jr., (1909-1990) was instrumental in collecting classical instruments, and the Bowman-Aminco spectrophotofluorometer is on exhibit here in the museum.

JA: Oh, is it?

MN: You haven't seen it?

JA: Yes, of course. It was in Building Ten. That's right. Bowman's an interesting guy, you know.

BW: Bowman's a genius. He's a genius.

JA: He's a physician, you know, but he liked to tinker. You know, when he was at Goldwater, he developed the flamephotometer to measure sodium.

BW: Really?

JA: Sodium in the blood, you know. Sodium is very important, the electrolytes, you know, with all kinds of diseases. Well, it was Bowman who built the flame photometer. He liked to do all tinkering, and he built this Aminco-Bowman spectrophotometer. Also, Sid was very much interested, Sid Udenfriend. He wrote a book on the spectrophotofluorometer in medicine. You remember that?

BW: Oh, very much so, yes. It has a Volume One and a Volume Two.

JA: Yes. Well, anyway, Bernhard and I collaborated on the LSD problem.

BW: Yes, and I had, at that time, relations with the discoverer of LSD, whose name is Albert Hoffmann. He was a research leader at Sandoz, and he described his exposure to LSD, which is active in micrograms. I think the normal dose of LSD that sends you into the beyond is about twenty-five micrograms, and the question was, how can you study the metabolism of something that is active at twenty-five micrograms? And probably, if you give much higher doses, they are lethal. So it was Julie's idea to use microsomes, and that did it.

I have the description of Hoffmann, who actually made the compound in '38, but he didn't get wise to the effect. But on April 16, '43, he weighed out some new LSD, and he made LSD, which is the lysergic acid diethylamide, because choramine, the nicotinic amide diethylamide, is a cardiac stimulant, you know. And he thought if choramine is active, then lysergic acid with a diethylamino group may also be active, and he didn't realize how active until he weighed it out and inhaled traces of it, and he said . . .

JA: Don't they put it on the tongue or something?

BW: Yes. No, he weighed it out, and then he said, "I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home, being affected by a remarkable restlessness combined with a slight dizziness. At home, I lay down and sank into a not-unpleasant intoxicated-like condition, characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed, I found the daylight to be

unpleasantly glaring. I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense kaleidoscopic play of colors. After some two hours, this condition faded away."

And apparently, this experience became known, and he wrote a book, which he dedicated to me, *LSD: My Problem Child.* And this way, he came into contact with Aldous Huxley, (1894-1963) who, by the way, last week, when we deplored the assassination of President Kennedy, that was the day when Aldous Huxley died, and he died—you know, he had cancer—with the help—he wanted to do that—of about 100 micrograms of LSD. So the transition from time to eternity was very pleasant, according to witnessing of his wife. But now, the LSD story is yours.

JA: Well, he wrote a book called *Doors of Perception*. Do you remember?

BW: That was his book.

JA: Well, you know, it's interesting, just at that time, I was giving a talk on my work at the New York Academy, and Huxley came in, and he tripped over the projector where my slides were. [Laughter] Well, anyway, it's an interesting story, you know, how LSD, Timothy Leary and all that . . .

BW: Gordon Wasson extended it, then, to—I mean, you were interested in mescaline first.

JA: Yes.

4BW: And Evarts worked with you, I worked with you, on mescaline, and then you extended it to LSD.

JA: Yes. Well, this is my introduction to mental health, you know.

MN: It's a great introduction.

JA: It was very colorful, but it really had no medicinal value. You know, many physicians used it. I think some actors–Cary Grant or something, used some of that stuff.

MN: Why did you start to study glucuronides?

JA: Well, that was another interesting story. I was just leaving the Heart Institute. I was going for my Ph.D. And I bumped into Jack Strominger, and I mentioned a paper by Dutton and Storey, two Scotch biochemists, who showed that in order to form a glucuronide, you need the cofactor uridine diphosphate glucuronic acid, UDPGA. "You know," he says, "I'll bet I know how that's made. It's made from uridine diphosphate glucose." He says, "Yes, and I have a method to measure glucuronide, because I found an enzyme—it showed how morphine formed a glucuronide." "But where can we get

some UDPG?" He says, "Well, you know, Herman Kalckar (1908-1991) is here, and he has some. Let's bring him into the problem."

And actually, I remember I did that experiment. I had a week before I had to go for my Ph.D., and I said, "this procedure requires uridine diphosphate glucuronic acid, a liver, and is it TPN or DPN?" We found that it was DPN. Its the color of morphine, you could see that. I remember that. And I left the problem, because I had to go to get my Ph.D. But Strominger had purified the enzyme, worked with Kalckar, etcetera. But the interesting part of glucuronide was, you know, Rudi Schmid was here, and he showed that jaundice was caused by bilirubin and how bilirubin was detoxified to prevent jaundice to form bilirubin glucuronide. He identified it.

I says, "Well, I'll bet I know the enzyme that can make it, because we have the cofactor." Jack Strominger and I just synthesized it, UDPGA." And so we added bilirubin and UDPGA in the liver. We found that it required TPN then. Well, anyway, so Castle at Harvard has a mutant strain of rats called a Gunn rat, which had jaundice. He said, "Well, we'd like to get some of those rats." And we found that the reason it had jaundice is they were very deficient in this glucuronide-forming enzyme. They couldn't detoxify bilirubin. That's another interesting clinical spinoff, you know, to some of the basic work.

MN: What made you change the direction of your research to go into psychoactive drugs?

JA: Well, it wasn't psychoactive drugs, it was mental health, but the reason I changed the direction of my research. I was very much interested in neurotransmitters. They had a very romantic history. I don't know whether you know this story. It was way back in 1904 that a student, whose name was Eliot—it wasn't T. S. Eliot. It was just Eliot—who was working for a very famous physiologist by the name of–it begins with an L. I can't remember it today. You know, my mind's going [J. N. Langley].

BW: You mean Sir Henry Dale?

JA: No. That's later on. It was–well, we'll call him L. [J. N. Langley. (1834-1906)]. Anyway, he was the one that described the sympathetic nerves, a very famous—but Eliot was a student of this guy. And Eliot found that—adrenaline was just isolated by a guy [John Jacob Abel (1857-1938)] from [Johns] Hopkins [University].

BW: Dale?

JA: No. Well, anyway, he [John Jacob Abel] isolated the active principle of the adrenal medulla elevated as adrenaline, isolated adrenaline, epinephrine, from the adrenal medulla. When Eliot injected adrenaline to a dog, they responded as if the sympathetic nerves were stimulated, and he proposed that perhaps nerves act by liberating a chemical,

like adrenaline, a chemical–there was a big argument, you know. At that time, the dogma was electrical transmission, you know.

BW: They had the dry school of pharmacology and the wet school of pharmacology.

JA: The wet and the dry. Well, anyway, in the abstract–he gave a paper at the British Physiology Society making his proposal, but his professor, he didn't believe in theories. He told him, "Forget about it. Don't mention it in the paper." And he actually didn't. But it struck the minds of a couple of investigators, particularly Otto Loewi (1873-1961, Nobel Prize 1936), who was a pharmacologist at Graz in Austria, who thought about this and said one day in a dream he dreamt of the experiment that proved chemical transmission. When he got up, he wrote it down on a pad, but Bernhard said maybe it was toilet paper. He couldn't read what he wrote. [Laughs]

JA: But anyway, he dreamt the same dream again, and he dashed to the laboratory with it, just an elegant experiment. What he did, he took two frog hearts. One was connected to the vegus nerve. He stimulated the vegus nerve, isolated frog heart in a bath, and it slowed the beat. He took the fluid and added it to another beaker, to a frog which didn't have the nerve, and that also slowed the beat. So he knew it was some chemical.

BW: Terrific experiment.

JA: Yes. Beautiful experiment. And it was Henry Dale who identified it as acetylcholine. Well that's one of the reasons that it has a fascinating history. And also it was interesting, you know, the psychological effects, and also clinically it was very important later on.

MN: How did you discover catechol-o- methyltransferase?

JA: Well, let's see now. Oh yes. Again, I got the abstracts of the Federation proceedings, the ones they used to hold at Atlantic City. I mean there's one here in Washington next year. I came across an abstract by Armstrong and McMillan, who found out that people have pheochromocytoma, which is a tumor of the adrenal gland. They excreted a lot of vamylmandelic acid, which is a catechol, which has a methyl group on a metaposition [of a catechol].

But anyway, that gave me an idea that perhaps epinephrine may be o-methylated because here was a tumor, an adrenal tumor, secretes a lot of adrenaline and here was this increase of an o-methylated product in the urine, so I suspected this may be one of the pathways for catechol metabolism by methylation. It was Cantoni who discovered s-adenosylmethionine, and I didn't want to ask him for any—I didn't think he'd give me any. But anyway, I knew it required ATP, methionine and magnesium, so I put that all together and I found a metabolite–a new metabolite when I did paper chromatography and I suspected it was o-methylated epinephrine, so I called up Bernhard, said, "Will you synthesize this?"

BW: And this is the scheme that convinced Stockholm that here is an achievement that deserves the prize.

JA: Well, anyway, so we had the pathway of the adrenaline, and of course we purified the enzyme—I became a pretty good enzymologist by then. I isolated catechol-o-methyltranferase and found that not only adrenaline, but dopamine and L-dopa, any catechol will be methylated. After that, maybe a year or two after Don Brown—you know Don Brown?

BW: Yes.

JA: He had a lab. He was a postdoc of Marion Kies. I was telling him about these methyl enzymes, and he was interested in histamine metabolism. He said, "Let's make some C-14 methyl-S-adenosylmethionine enzymatically." We did it in a couple of days. That means anytime you add the C-14 labeled S-adenosylmethionine, the product will become radioactive. We discovered a couple of enzymes protein-carboxy-methylations. One of the nice things about NIH, you know, you could collaborate with people right away. I know it helped you a lot.

MN: I had some wonderful collaborations.

JA: Yes, you know Maxine Singer made the nucleotides for you, yes.

MN: Oh, absolutely. Absolutely.

BW: But Julie was in the shadow of Brodie. It was very hard to find out that you were the one who found out what reserpine does.

JA: Well, no, I didn't, really. No. I don't want to claim credit—it was actually Parkhurst Shore. I don't know if you remember him.

MN: I remember him.

JA: Parkhurst Shore had a discussion with Herb Weissbach, he suspected it was serotonin at that time, and Herb and Sid were working on metabolism of serotonin and said "Why don't you look for hydroxyindoleacetic acid in urine after you give reserpine," and he found, when he gave reserpine, a big elevation [in hydroxyindolacetic acid] and they knew it was depleting serotonin.

BW: And then they found out that Herb Weissbach had so much of this metabolizete of serotonin in his urine, that they wondered and found out the reason, because he ate two bananas in the morning, and bananas are full of serotonin, and this got Udenfriend into contact with United Fruit. He got an invitation from United Fruit.

JA: Maybe it should be an antidepressant, because you know how it works, it elevates serotonin. To hell with Prozac, eat bananas. [Laughs]

BW: You discovered the reuptake of norepiniphrine, didn't you?

JA: Yes. Well, yes. To follow, I'll get to that in a minute. We found metanephrine and all the metabolites with Bernhard's help. We'd get collaboration. Well, anyway, what happened, we found an inhibitor for catechol methyltransferase. It's been shown by this Swiss guy who worked on MAO—what's his name? Starts with a K [may be Keller]. He found an inhibitor for MAO. He found that it didn't inactivate epinephrine. You know who I mean.

BW: Yes. May be Alfred Pletscher of Roche?

JA: But he was someplace here. But anyway, when MAO was inhibited and COMT was inhibited, and you would inject adrenaline, noradrenaline. Usually when you inject it, it raises the blood pressure and goes down very fast because of these two enzymes. However, when we knocked out those two enzymes, inhibited them, and we injected norepinephrine, the blood pressure still went way down [rapidly]. Something was inactivating the effects of norepinephrine and it wasn't those two enzymes, because they weren't working. They were inhibited.

So, well, what do you do? It was something new. Well, one of the things I did when I worked with Brodie, I studied the distribution of drugs, where it went, and at that time Kety became head of the laboratory. Evarts stepped down. He didn't want to be the director of the Mental Health anymore; he stepped down. Kety gave a very interesting seminar describing the work of two Canadian psychiatrists, Hoffer and Osmond, saying when they let adrenaline stay out in the air, it turned pink, formed adronichrome, and when they—they took it themselves. They said they hallucinated. I was fascinated by this. Hallucinated. And they proposed that hallucination is caused by an abnormal metabolism of epinephrine adrenaline, because of adrenochrome.

So I spent four frustrating months trying to look for the enzyme that could convert adrenaline to adrenochrome and I could never find it. It was a lot of crap. But anyway, Kety wanted to test this hypothesis. He ordered some tritium labeled adrenaline because I already, with Bernhard's help, worked out all of the metabolites, the whole pathway of noradrenaline and dopamine. He wanted to see if those who have abnormal metabolism of adrenalin were schizophrenics—we had a ward with schizophrenics that get tests anyway. Well, anyway, I asked asked him for some. I wanted to do a distribution of adrenaline and noradrenaline because doing the endogenous [compound] is very difficult. So we injected radioactive adrenaline into a cat, and generally, you know, epinephrine was very rapidly metabolized, but what we found is that after two hours, there's a lot of

adrenaline still in tissues, almost as much as after 2 minutes—and we suspected that somehow it was sequestered someplace.

I had a very good visiting scientist, a real good pharmacologist, George Hertting from Vienna, came for a couple of years to my lab, and we had big discussions. Why did it [epinephrine] stay around? Where is it going? And we found that generally it was highest in tissues like the heart and the spleen, that were heavily inervated by sympathetic nerves–these are noradrenaline containing–and we suspected it may be going into these nerves so how do you prove it? Hertting had a brilliant idea. You know, when you remove the ganglia, the superior cervical ganglia, pluck it out at one side, all of the nerves on that side disappear; they'd disintegrate. So you had a cat which had nerves intact on one side and absent on the other side. When we injected radioactive noradrenaline, all the radioactivity was on the inervated side. So we knew that it was going back into the sympathetic nerves.

Another experiment, what Hertting did is infused radioactive noradrenaline into the splenetic artery. It was a very complicated preparation which I could never do, having to avoid any artifacts.... So we stimulated the, I think the splenetic, nerve–it released the radioactive noradrenaline, so it was taken up and released. The whole process, it was a very novel phenomena, you know. That was 1959. But what we did then to see how would drugs affect reuptake, so what we did, one of our first experiments we did is give cocaine and then inject radioactive noradrenaline. We found the tissues such as the

spleen, all the radioactivity was way down when you gave cocaine, because it blocked reuptake. And the same thing with amphetamine. But we wanted to know what happened in the brain, so Jacques Glowinsky, who was a postdoc, he found a way to introduce radioactive noradrenaline in the brain, in the lateral ventricle. So what we did, at that time the antidepressant drugs we used were imipramine, desipramine, amitriptyline.

So we got some from one of the drug companies, a whole series of tricyclics, some of which were clinically active in depression and some which were not. So while we introduced--injected--these drugs and then gave radioactive noradrenaline, all the clinically active tricyclics lowered the noradrenaline in the brain, so it blocked the reuptake, the phenomenon of reuptake. And later on, of course, they showed this could block serotonin and dopamine, this is how Prozac and Zoloft and Paxil were developed, saved the drug companies millions of dollars. Instead of testing them on humans, they can test them on rat brains and tell where there was going to be a potential, at least, of antidepressant, before they could test it. They saved a lot of money that way.

MN: It opened up a whole field of research.

JA: Very rapid development, a rapid introduction of antidepressant drugs, you know. Prozac, Paxil, and Zoloft and all of that. Yes, that was, again showing how basic work translated

to a clinical... and make drug companies a lot of money, too. Particularly this Medicare bill they're going to pass today will make the drug companies a hell of a lot of money.

BW: Another candidate for the biochemical basis for schizophrenia was 6-hydroxydopamine, and Hans Thoenin at your lab found out how it works.

JA: He found out—no, that's an interesting story. Hans Thoenin, he as working for Hoffmann LaRoche in Switzerland. He was working sort of a very, very boring kind of work he was doing. He wanted to spend a year in my lab. I said, "You can come if you can bring 6-hydroxydopamine." What he found, that 6-hydroxydopamine, it was in Berne or something. Well, anyway, when he gave 6-hydroxydopamine, it destroyed catecholamine nerves. I said, "Bring that with you."

So what we did, we gave 6-hydroxydopamine to a rat. We found that tyrosine hydroxylase levels went way up. What 6-hydroxydopamine did is stimulate–this is the adrenal gland–it stimulates the sympathetic nerves. It stimulates the enzyme that makes dopamine and noradrenaline, goes up, and that's what we found.

BW: The 6-hydroxydopamine was first made by Hans Thoenin. And then John Daly got interested in it.

JA: He didn't know what it did, though.

MN: Well, I think it was Sjoerdsma at that time who worked with Udenfriend, and he gave it to dogs and he said, "Don't give me that stuff. It ruins my dogs." [Laughter] So we didn't research this any further.

JA: Well, anyway, yes, okay. Let's go on.

MN: Tell us about your work with Herb Weissbach on the biosynthesis of melatonin. That's an interesting thing.

JA: That was an interesting story, too. I occupied many–after I won a prize on . . . I came across a paper by Aaron Lerner at Yale, a very good biochemist as well as dermatologist, and he found that if you add [bovine] pineal extract to tadpoles, it will blanch the skin. Aaron thought that maybe—what is the active principle of the blanching? He isolated the active principle that he identified as melatonin, which is serotonin with a methyl group on it. I saw that paper. I was fascinated of course because I was working on methylation reaction.

And Herb Weissbach was working on the metabolism of serotonin at that time, so I had lunch–over here at the cafeteria where you meet people, you exchange ideas. We'd talk, and we had an idea, let's see if we can find the enzyme that makes melatonin by using radioactive S-adpnosylmethionine with serotonin. We found the enzyme. It was a

pineal. It was highly localized in the pineal. So we found that enzyme, and not only that, it led to some other very interesting findings. It was discovered there was a serotonin rhythm in the pineal gland. It was low at daytime, high at night.

MN: Circadian rhythm.

JA: Solomon Snyder was then a postdoc of mine in the lab, and we didn't have a method for melatonin. Let's see whether this rhythm is a self-generating rhythm, a circadian rhythm." So we developed a method for serotonin [a precursor of melatonin], and we found that this rhythm of serotonin, if you cut the nerves to the brain, it will stop, this rhythm, so we knew there was a signal coming from the brain for this rhythm, serotonin.

There was actually at that time just—what's his name again? Bob Moore. He was then at San Diego, I think. He found the suprachiasmatic nucleus was the biological clock in the brain, that causes not only the melatonin rhythm, but also a lot of other rhythms. It's a big thing, you know, circadian. You have many genes involved in this biological clock. I don't know whether you're familiar. But anyway, one thing about working with the pineal gland, you know, almost all experiments worked. Every time I came depressed with working on other problems, I worked with the pineal, I always got a successful result. It lifted my spirits, my personal antidepressant. [Laughs]

Anyway, I found it fascinating. Recently they found how light can affect the serotonin rhythm. It has to come from the outside, you know, to affect this rhythm. Also one of the things we did with Solomon Snyder is when we kept in the complete darkness, the serotonin rhythm still persisted, so there was an endogenous clock. It was found later on the same thing with melatonin. And they found just two years ago, right across the street at the Naval Medical School, they found an opsin, a new opsin, melanopsin. Have you heard of it? Melanopsin. Actually, light reaches to the pineal through melanopsin without the rods and cones.

MN: That's fascinating. It really is. One of the most impressive things that I found is that over much of your career you've worked in the lab yourself and done your own experiments.

JA: Yes.

BW: How did that work? How many people did you work with?

JA: Oh, well, altogether I never had more than three or four postdocs, but I had a long career with about sixty people. I had visiting scientists and postdocs. I think I learn more from them, as much from them, as they learn from me. I think this interaction—I'm sure you all have had that experience.

MN: Absolutely.

JA: Working with bright people, you just trigger ideas, you know, talking and experiments, what kind of experiments are critical, and all of that. Are we being taped now?

MN: Yes.

JA: Yes, I find that I'm sure so many people came out of your lab, particularly, Gilman and that fellow from Harvard.

MN: Phil Leder, yes—wonderful people to work with.

JA: One thing about—you know, I don't think I could have done what I've done anyplace else but here. I was given complete freedom and just marvelous resources, both physical resources and intellectual resources. Nothing like it here.

BW: But Julie, in his modesty, was asked in '69 and he said, "Well, I have been at the Institute of Mental Health for five years, and I haven't done a thing for mental health." That was the year after, when he got the Nobel Prize. [Laughs]

MN: I think that the basic findings that you made in neurochemistry are fantastic, and they've led to many things that are clinically used these days.

JA: I think the greatest satisfaction that I have, aside from making these basic discoveries, that it had clinical implication in pain and depression. This, I think, is the most satisfying thing I've had.

MN: Most of the current medicines that are used for depression came from your basic findings.

JA: Yes. But I think people don't understand the value of basic research and what it leads to. I think that passage you just showed me of Arthur Kornberg is a good example.

BW: When they closed the Roche Institute of Molecular Biology, I told Herb Weissbach, well, basic research is so important and nobody has formulated it better than Arthur Kornberg, who got his Nobel Prize as early as 1959, and he said, "The difficulty with research support in our society, I have come to realize, is the failure to understand the nature and importance of basic research. This failure can be seen among members of the lay public, political leaders, physicians, and even scientists themselves. Most people are not prepared for the time scale of basic research and the need for a critical mass of collective effort. Fragments of knowledge unwelcomed and unexploited are lost as were Gregor Mendel's genetic discoveries.

"The vast majority of legislators and some scientific directors cannot accept the seeming irrelevance of basic research. Were there a record of research grants in the Stone Age, it would likely show that major grants were awarded for proposals to build better stone

axes, and that critics of the time ridiculed a tiny grant to someone fooling around with bronze and iron. People do not realize that when it comes to arguing their case for more funding, scientists who do the basic research are the least articulate, least organized, and least temperamentally equipped to justify what they are doing. In society, where selling is so important, where the medium is the message, these handicaps can spell extinction."

JA: Again, just this conversation we had, this example of how basic research led to discoveries that helped people, you know, over their afflictions. I think it's a pity that the funding for the NIH has been so drastically reduced. I think it's a shame. It will show, I think, with future discoveries.

MN: Do you have any advice to young scientists?

JA: Well, there's a German expression about research. It's "glück, geduld, und geld [luck, patience, and money]."

MN: Three Gs. That's Paul Ehrlich.

JA: Well, yes. I think there are so many ways that one can do science. Depends on your temperament, your style, and you don't need a great brain or have all A's in your subjects. You have to have an imagination; you have to ask the right questions; you have

to have a mentor that can inspire you. I would recommend, if you have the talent and the capacity to do it, it's a great life. I think we can all attest to this.

MN: I can second that.

JA: Thank you.

MN: Well, thank you very much.

[End of interview]

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