

Interviewee: SEYMOUR KETY
Interviewer: IRWIN J. KOPIN
Date: December 12, 1995
Edited: Kety(Kopin)-Kopin-Kopin-Ban

IK: I'm here to interview one of my major mentors in science, Dr. Seymour Kety. Dr. Kety was born in Philadelphia, went to Central High School and to the University of Pennsylvania. He had training in Boston with Joseph Aub, went back to the University of Pennsylvania where he made some major contributions to studies of blood flow to the brain, then came to the NIH, first as the scientific director of what was then precursor of two different institutes, called the National Institute of Mental Health, which, at that time, included the National Institute of Neurological Disorders and Blindness, among other things. Somewhere around 1956, he stepped down to lead the Laboratory of Clinical Science. The Laboratory of Clinical Science has spawned some of the last century's greatest scientists, including Nobel Prize winner, Julie Axelrod, many members of the National Academy of Science and was the spawning ground of, I would say, at least half of the psychiatrists who were interested in biological psychiatry. I regard, and I think everyone else does, Dr. Seymour Kety as the father of biological psychiatry in this country, certainly, if not the world, and it's indeed a pleasure for me to have the opportunity to try to elicit from him some of his early memories of his science and the major contributions that he's made over these many years. Seymour, can you tell us how you got started in going from your early years, during internship and research on lead poisoning, how did that trail lead to your later research. You went to Boston with this background but soon you returned to the University of Pennsylvania, tell us a little bit about that.

SK: I got interested in lead poisoning because I had a summer job with a biochemist and toxicologist in Philadelphia who was doing a project for the lead industry, in which it was necessary to analyze the urine of some of the men who worked with lead. I was given the job of analyzing the urine and in the analysis; one used sodium citrate to dissolve the insoluble lead compounds. And, it occurred to me that, maybe, sodium citrate would be useful in the treatment of lead poisoning. And, when I was in medical school, I tested that possibility for a paper to be presented at a Student Research Day by feeding rats food contaminated with lead and, then, giving them water with sodium citrate added. Then, analyzing their urine and comparing that to the urine before they had an opportunity to have sodium citrate, we found that the urine lead content went way up with the sodium citrate. Then, when I was an intern at Philadelphia General, I spent my evenings doing some studies in the laboratory there and one of the studies that I concentrated on was an examination of the lead citrate complex. I published my first paper, as a matter of fact, in the Journal of Biological Chemistry, which was a characterization of the lead citrate complex. Later, Letonoff and I administered sodium

citrate to some patients at the hospital, who were suffering from lead poisoning. Letonoff was measuring lead in the urine and lead-blood-levels and found that the sodium citrate did have a therapeutic effect. That, I think, was the first treatment of lead poisoning with a chelating agent. Of course, shortly after that time, much better chelating agents were developed and lead poisoning has been treated with these more powerful chelating agents ever since. As a result of that lead study and my interest in lead poisoning, I applied for a National Research Council fellowship to work with Dr. Aub, Joseph Aub, in Boston, who was the national expert on lead and lead poisoning. I won this fellowship and spent a year in Joseph Aub's laboratory at the Massachusetts General Hospital, which was a very interesting year. Dr. Aub was a great man. He was professor of research medicine at Harvard and at Mass General. We didn't do much on lead poisoning; however, because of the imminence of the war, World War II.

IK: This was about 1940?

SK: I went to Aub's laboratory in 1942, from '42 to '43. That was before America got into the war, but the war was imminent and I had attempted to enlist in the Medical Corp, but the army rejected me because of an old fracture that I had with some infection of the bone, whatever reason. But, Dr. Aub's laboratory was working on shock, not on lead poisoning, so I participated in that. There was another post-doc in Dr. Aub's laboratory, Alfred Pope. He and I were the two low men on the totem pole and we spent many evenings together taking care of the dogs who were in shock, taking their blood pressure regularly and so on.

IK: That must have been a rough year for you, because you were married then and you were shuttling back and forth to see Josie in Philadelphia. Is that right?

SK: I married Josephine in 1940, just before my internship, and Josephine joined me in '41, becoming an intern at Philadelphia General Hospital, as I was. And, then, she did her second year of internship while I was in Boston. Since that internship was a pretty rigorous period in which one spent a lot of time, a lot of evening in the hospital, it really wasn't too bad, because I would come back to Philadelphia on weekends.

Pope and I became interested in the physiology of shock and we wrote a paper, which was published in the American Heart Journal, on the homeostatic reflexes involved in shock for the purpose of preserving blood flow to the brain. That got me interested in the importance of the cerebral circulation. At the same time, I read a paper by Dumke and Schmidt. Schmidt was my old

professor of pharmacology as a medical student, and this was a paper in which they were measuring measuring cerebral blood flow in the rhesus monkey by using an ingenious bubble flow meter, which had been developed by Rachmael Levine. These, I think, were the first really reliable quantitative measurements of cerebral blood flow in at least in lower animals. And, I decided I would be returning to Philadelphia at the end of my fellowship. I had written to Carl Schmidt, asked whether I could work in his laboratory. He offered me a position there, and I came back and worked with him on the study he was doing, which was the metabolism of the brain of the monkey, using, the bubble flow meter. But we also measured arteriovenous oxygen differences and studied the metabolism in various states of wakefulness, anesthesia, convulsions and so forth. Around that time I began to think that although these studies in the monkey brain were interesting, they really didn't have the fascination that the possibility of studying the human brain, circulation in the human brain, meant to me. This, I felt, would be a much more important thing to do, because it is the human brain, which is heir to disorders that one cannot produce in lower animals like schizophrenia and other mental illnesses, it is the human brain that experiences profound sorrow, laughter, jests, incites, and it's the human brain that can speak and reveal its' inner workings to some extent.

IK: At the time there were also other people interested in similar problems. There was Himwich, and some of the people in Boston, who were measuring arteriovenous differences in oxygen. They were using the same data but came to different conclusions or interpretations. Weren't they?

SK: Yes, that's right. A Boston psychiatrist, Myerson, had developed a means of getting venous blood from the human brain by putting a needle into the internal jugular around the mastoid process. Since they were able to get cerebral venous blood and were able to tap an artery to get arterial blood, they could measure the arteriovenous oxygen difference across the brain. And, Lennox and Gibbs, working at the Boston Psychopathic Hospital, which is now the Massachusetts Mental Health Center, studied cerebral circulation by merely examining the arteriovenous oxygen difference and using the Fick equation which, as you know, states that the blood flow through the body or through an organ is equal to the amount of oxygen taken up by that organ, divided by the arteriovenous oxygen difference. Now, they weren't able to measure the oxygen consumption of the brain, but they were able to measure the AV difference. So, if you assume that the oxygen consumption is constant then the AV difference is inversely proportional to the blood flow. And, so, with that expedient, they would study cerebral blood flow under the influence of carbon dioxide, in epilepsy

and in a number of other conditions.

IK: They kept the numerator constant by fiat, by deciding that it was valid. And, Himwich did just the opposite, nominally.

SK: Himwich was interested in metabolism rather than blood flow, because he was studying mental retardation and other mental disorders. And, he used the AV difference as a measure of the oxygen consumption with the assumption that the blood flow is constant. Well, the difficulty with both of these techniques is that the AV difference is the result both of oxygen consumption and of blood flow to the brain and one cannot measure either one of these without knowing.....

IK: You've got one equation with two unknowns.

SK: Exactly. You have one equation with two unknowns, and that was a problem.

IK: Didn't this lead to some funny results, as for example with anesthesia?

SK: By and large, they guessed right. Although, they weren't able to make absolute measurements, they would make qualitative measurements.

IK: Well, what was the conclusion that they reached with anesthetics?

SK: Well, they made some false assumptions. With the anesthesia, the AV difference diminished. We know now the AV difference diminished because the oxygen consumption went down. But in their assumption that the oxygen consumption was normal, the AV difference diminished simply because the blood flow increased. So they assumed that there was an increase in blood flow with anesthesia.

IK: A huge increase.

SK: Yes, doubling. But, by and large, they guessed right. But, of course, they could never be sure and the problem was that oxygen is a poor tracer to use in a situation like that, because oxygen, is used by the brain, and used in different amounts under different states. In fact, in the very state that one is studying, the oxygen consumption may vary. And, so, I thought, well, why not use a gas that, unlike oxygen, isn't metabolized. The amount of that gas that would be taken up would be the result of purely physical properties like the solubility of the gas in brain tissue, the principals of diffusion from capillary into the tissue. These factors could be independent of whether the brain was thinking or sleeping or suffering from one or another disease that didn't effect seriously the solubility of a gas in the brain. When I was in Boston, I'd attended a number of "shock dinners" that the people in Boston, working on shock, used to have, including all the staff of Dr. Aub's laboratory.. We would

invite outside speakers to these dinners, and these lectures were supported by the Macy Foundation . On one of these occasions, Andre Cournand came up to Boston to give us a talk on his studies of cardiac output in human veins, using the Fick principle. He was measuring mixed venous blood by inserting the catheter through an antecubital vein to the right atrium. This was a very impressive lecture, because it was obvious that he was studying, in human veins, physiological parameters and measuring them more reliably and more accurately than they had ever been done in animals by using an indirect technique which was minimally invasive, certainly, not as invasive as a surgery that was required in most of the studies in animals. So, that convinced me that it was possible to study, in human subjects, these physiological processes with indirect methods that were less invasive than one used in animals. The inert gas that I finally selected was nitrous oxide. Physiologists, before me, had used nitrous oxide as an inert gas for studies of cardiac output and for pulmonary function studies. I spoke to Dr. Stady at Penn, who was an expert in this area, and learned that nitrous oxide would be very nontoxic in human beings. At a concentration of fifteen percent, the subjects would not experience any anesthesia. That was the beginning of the nitrous oxide technique for measuring cerebral blood flow. I went to the Philadelphia General Hospital and practiced getting blood from the internal jugular, using the Myerson technique on cadavers and after I felt that I was proficient enough in that, I approached a patient in the neurology building, a patient, who had been in that building for years and was very happy to find a physician interested in talking to her and in studying her.

IK: At that time the Philadelphia General Hospital was like part nursing home, wasn't it?

SK: No, the neurology clinic, the neurology building was more than a nursing home. It was a museum of neurological disorders and it was just full of patients who had all sorts of neurological disorders and lived in the hospital most of their lives. And, this lady was very gracious and very cooperative and was perfectly happy to have me study her cerebral circulation as I told her I was interested in doing. So, I did the first nitrous oxide study with her cooperation. I got curves of the nitrous oxide concentration in femoral artery blood and in internal jugular blood. And, as a matter of fact, I published this pair of curves in my first paper.

IK: The pair being the arterial and the venous, right?

SK: Right. Now, with those two curves, it was simple enough to get the arteriovenous difference, but the difference was not constant as it would be with oxygen. It was a variable, because the brain

came to equilibrium with nitrous oxide at the tension in the arterial blood eventually. And, so, the AV difference started wide and, then, gradually narrowed down as it went along. So, one could integrate the AV difference and get the amount of nitrous oxide taken up by the brain.

IK: That was the area.....

SK: That was the area between the two curves, over a period of time. But, how does one get the numerator of the Fick equation, the amount of nitrous oxide taken up by the brain? Well, if one waited until the brain was in practical equilibrium or close to equilibrium with the blood which was exiting it, which turned out to be about ten minutes on the basis of calculation and on the basis of studies in dogs, in ten minutes the venous blood emerging from the brain was in practical equilibrium with the brain tissue itself.

IK: It's same concentration as the arterial?

SK: No, it wasn't the same as the arterial in ten minutes. We saw a little AV difference, but all it had to be in equilibrium was the venous blood, because someone could take the venous concentration and with a partition coefficient representing the difference in solubility could calculate, not the amount of nitrous oxide in the brain, but the concentration of nitrous oxide in the brain. That's why the value for the blood flow emerged as the blood flow in milliliters per hundred grams per minute. I, then, explained this to Carl Schmidt, showed him this curve and told him that I would like to apply this technique to studies in patients in the hospital at the university. Carl suggested that it would be a good idea to calibrate this technique against cerebral blood flow as measured with the bubble flow meter. I agreed, and, together, we did exactly that. Carl set up monkeys with the bubble flow meter and I set them up to use the nitrous oxide technique and we found that there was a good correlation between the values obtained by the nitrous oxide technique and those obtained with the bubble flow meter. And, so, with that assurance, I published the first paper on the nitrous oxide technique with Carl Schmidt. That was in about 1943. And, then, we studied cerebral blood flow and cerebral oxygen consumption, because once one had the blood flow and the AV difference, one could calculate the oxygen consumption. I measured these functions in a series of normal volunteers. These were men who were conscientious objectors and who decided to volunteer for human medical biological studies as their way of contributing to the scientific community. It was also their social contribution in the wartime. And, we published the values in these normal young men for cerebral blood flow, oxygen consumption. It turned out that the oxygen

consumption of the resting human brain, from which one could calculate the energy released and the power.....

IK: Did you do glucose utilization at this time, also?

SK: No, we didn't do glucose utilization at first, but we did glucose utilization shortly afterwards in normal controls. And, with the glucose utilization and the oxygen utilization, we could calculate the energy release and that turned out to be the equivalent of the energy utilized by a 20-watt incandescent bulb, which was a remarkably small amount.

IK: It was a dim light.

SK: It was a dim bulb compared to the huge amounts of energy, which was necessary to feed the computers at that time. Of course, since 1942 or '43, the computers have become miniaturized and the energy utilized by them much less. So, I suppose, it won't be very long before computers will be developed that will utilize 20 watts of energy and perform the kinds of functions that the human brain is capable of doing.

IK: Well, how did you come to NIH? This was one phase of your career. I think that was a time when you were getting interested in, I suppose, mental disease or at least how the brain worked. What stimulated the transition to the NIH?

SK: I moved from Carl Schmidt's department to join Julius Comroe, who was my true mentor in the period that I spent at the University of Pennsylvania. Julius Comroe was a great physiologist of the pulmonary system, the lungs and respiration.

IK: Was he, in any way, the mathematician in the marvelous review that you published on diffusion of gases, which has really been a classic?

SK: No, Julius didn't make any pretenses of being a mathematician. And, as a matter of fact, I wasn't much of a mathematician until I got interested in working out the theory of the nitrous oxide technique where I had to go back and brush up on calculus and so on. That review, I wrote because Goodman and Gilman, who were editors of the Pharmacologic Reviews asked me to write a review on the exchange of inert gas between blood and tissue, and I thought that was an interesting thing, something I wanted to do anyhow. And, I spent a year reviewing the literature and tracing the development of our knowledge of the exchange of inert tracers between blood and tissue. In the course of that, I made some original contributions, for example, calculated, in a more extended fashion, the uptake of ether by the human lungs, and circulation, and brain, using a much more exact

replica of the situation than Haggard had used, who was the first person to attempt to write an equation for the uptake of ether. The equation that I came up with was a more exact equation than that and, in fact, with that equation one could relate the speed of induction of inhaled anesthetics on the basis of their solubility in blood and on the basis of physiological parameters like ventilation and cardiac output and so forth. I also addressed the question of the exchange of inert gases or inert tracers between the capillaries of the brain and brain tissue itself, and derived an equation that was going to be of great importance to me in a few years time.

But, you asked about how I came to the NIH. Just about the same time that I finished that review and sent it in for publication, it was published in 1951, I had a visit from Bob Felix, who was the new director of a new institute of the National Institutes of Health, the National Institute for Mental Health. He came to ask me if I would be interested in joining him in the new institute as the scientific director of the Mental Health Institute and we had a nice conversation. And, I thought he was a lovely man and I felt that it was going to be difficult for me to turn him down because he was such a generous person, but I knew that I wasn't going to work for the government. I was perfectly happy working in academia and working at the university with Julius Comroe. But, he urged me to go down and visit the National Institutes of Health and I went down with Josephine and Bob Felix showed me the Clinical Center, which was still in the stage of construction, walked me through the laboratories that the Mental Health Institute was going to have and talked to me about the challenge of directing the greatest program for the study of brain and behavior that the world had ever seen. These were his words. Well, it certainly was the largest program, contemplated for the study of these functions that the world had ever seen. Whether it was going to be the greatest was to be seen later. In any case, I came down and I met with the people at the Mental Health Institute, John Eberhart and others, who were working with Bob Felix in this new institute, which hardly had a place in which they could work to do their administrative work, and I met the scientific directors of the other institutes. I remember talking at great length with Jim Shannon, who was scientific director of the Heart Institute, and Harry Eagle and a number of the other scientific directors and, somehow, I became convinced that this was a challenge and an opportunity that I couldn't turn down. So, I joined Bob Felix in 1951 as the scientific director of the Mental Health Institute. By that time, it was also decided to start another new Institute, which was to be the Neurology Institute, and it later became the National Institute for Neurological Disorders and Blindness. And, so, I was scientific

scientific director of both of those Institutes at first, because the Neurology Institute was grown out of the Mental Health Institute as Eve grew out of Adam's rib. Bob Felix had become interested in talking to me because of the nitrous oxide technique and because I had done a study with collaborators of schizophrenia, which was published in the American Journal of Psychiatry. Bob, with a little prompting by the directors of the NIH, had decided that it would be a good idea to get a scientist as Scientific Director of the NIMH and since the Neurology Institute was also to be part of the affiliation that it would probably be a good idea to get somebody interested in biology. And, when he saw the paper on Cerebral Blood Flow in Schizophrenia, he thought that I was his man. And, so, we came down in 1951.

IK: That was a full four or five years before you ultimately stepped down from that position.. At the time, you were recruiting people into the two Institutes.

SK: That was a very exciting period. I began to establish the organization of the Intramural Program of the NIMH and, also, to lay down the philosophy. I decided right off the bat that biology was going to be of considerable importance in psychiatry and in the study of mental illness, because I was convinced that the brain had a great deal to do with mental illness. At the same time, I realized that our knowledge of the biology of the brain was very rudimentary and there were a lot of half-baked studies on biological aspects of schizophrenia. People would come up with great new discoveries of chemical changes in the blood that they found in patients with schizophrenia and these were all premature and very difficult to replicate and none of these were ever confirmed. They just appeared in the Sunday supplement of newspapers and they disappeared very quickly. It was obvious that what we needed was a great deal of basic research. We needed much more information about the fundamental aspects of the processes, the biological processes in the brain, before we could even think of attacking the practical problems. What we needed was, if we were to build a bridge across a big chasm between basic knowledge of the brain and mental illness, to firm up the foundations of the bridge on both sides. We had to firm up the knowledge of basic information about the brain and we had to firm up our knowledge of the mental illnesses itself before we could upgrade the cross between them.

IK: Who were some of the people that you had brought in between 1951 and 1956?

SK: All right, that was a very exciting list of people. The first laboratory that I set up, interestingly enough, having said all this about biology, was the Laboratory of Socio-Environmental Studies. I

set that up because that was a field that I knew least about and, also, because I wanted to make sure that we didn't forget about the extra biological factors that determine mental illness. I sought for a director of that laboratory and found that we had an outstanding sociologist of mental illness, who was already working with Bob Felix at the NIMH and that was John Clausen. So I made John Clausen director of Socio-Environmental Studies. Seeking a director for neurophysiology, I discovered that working quietly in the Mental Health Institute, before I got there, was an outstanding neurophysiologist, Wade Marshall. He was the person who laid the groundwork for the studies of the cerebral cortex, the motor and sensory cortex, which was pursued eventually by Rose and Bard working with Wade Marshall. By that time, Wade Marshall was at Johns Hopkins and worked with Rose and Bard on this subject, or began to work with them on this subject. Then, Wade became seriously ill and he left that project and Rose and Bard went on to pursue it. They made these beautiful maps of the cortex of the cat and the monkey, which was then followed by studies on the human cortex by the neurosurgical group in Montreal. By the time that I got to the NIMH, Wade Marshall had been discharged from the hospital, had gotten a job with Bob Felix in neurophysiology, and was doing some very nice work on the cerebral cortex.

IK: At this time, there was the beginning of the revolution in pharmacology and in psychiatry. Wasn't chlorpromazine being introduced as the first antipsychotic?

SK: Well, as a matter of fact, chlorpromazine was introduced in the United States around 1952 or '53.

IK: Right.

SK: In '51, it was being studied in France, yes, and greatly utilized. I made Wade Marshall chief of Neurophysiology and that was a very good appointment, because Wade turned out to be an excellent chief and passing through his laboratory were some of outstanding neurobiologists.

IK: Evarts, Eric Kandel.....

SK: Evarts and Kandel and, also, Bill Landau and Lewis Rowland, who became two of the outstanding professors of neurology in the country. I appointed Giulio Cantoni to this new Institute as head of a Laboratory of Comparative Pharmacology, and he brought Seymour Kaufman into his laboratory. When I appointed these people, the understanding was that they did not have to work on mental illness. They didn't have to promise to work on the brain. They were supposed to work on what they felt was important and on what they felt would ultimately be of importance to an

understanding of mental illness, but it was up to them to choose the direction in which they went.

I also appointed Bill Wendell as head of a Neuroanatomy Laboratory and he readily appointed Sandy Palay as one of his section chiefs. Palay became an outstanding electron microscopist of the brain. Alex Rich came to see me about a position at the NIMH from Linus Pauling's laboratory and Alex impressed me very much by talking to me about the macromolecules of the brain and how protein synthesis might be taking place and how the proteins might be responsible for encoding memory. He impressed me thoroughly, and I had a long conversation with Linus Pauling on one of his trips to Washington, I remember sitting on a park bench outside of the hotel where Linus was staying, and get Pauling's generous recommendation of Alex. So, Alex came in as chief of a Laboratory of Physical Chemistry and he brought into that laboratory a number of outstanding molecular biologists, who, went on and pursued their own careers in a very imaginative way. Julie Axelrod came to see me from Steve Brodie's laboratory in the Heart Institute. He came to see if there was an opportunity to join this new Institute, the Mental Health Institute, and, actually, he thought that he would like to work in Dr. Cantoni's laboratory because Cantoni was the pharmacologist in the Institute, head of the Laboratory of Comparative Pharmacology. I didn't think that was such a good idea because Axelrod was interested more in the applied side of pharmacology, the development of drugs, the metabolism of drugs and the metabolism of hormones, and these were not the areas that Cantoni was particularly concerned with. But, by that time, I had also appointed the head of clinical research in the institute. This was Bob Cohen, who was a psychiatrist and a psychoanalyst, from Chestnut Lodge and he was developing the clinical program, which was very largely non-biological. I thought it would be a good idea if Bob were to have a laboratory on the clinical side that was interested in biology. Bob had already started such a laboratory with two people, Marion Keyes and Ed Evarts, and was also working with Wade Marshall at that time. So, I called Steve Brodie to make sure that he knew that I was thinking of offering Axelrod a position with our institute. We didn't want to rob another Institute without letting them know.

IK: Julie had just gotten his PhD recently, hadn't he?

SK: No, he hadn't gotten his PhD. And, I referred Julie, then, to Bob Cohen. I sent them a memorandum saying that I had seen this man and he looked like an extremely attractive individual. It would be a good idea if he could give him an appointment in the laboratory that he was developing in the clinical side. And, so, Julie joined the NIMH working in that clinical program. By that time, I

had asked Lou Sokoloff, who had been working with me at Penn to come down to NIH and join me. I set up a Laboratory of Cerebral Metabolism and made Sokoloff chief of a Section in that Laboratory. That was the Laboratory where I hoped that I would do some research, in addition to the task of organizing the Intramural Program. In 1956, I felt that I had done my share. I'd spent five years organizing the Intramural Program, recruiting an outstanding group of people, and I spoke to Bob Felix about the possibility of stepping down from that position of scientific director and become a laboratory chief. Bob was very generous, he saw the possibilities there, and permitted me to step down. I became chief of a new laboratory, which had already been started with Ed Evarts, Julie Axelrod, Roger McDonald, Marion Keyes and Roger McDonald, who was nominally the chief. He had decided to call it the Laboratory of Clinical Science. They were all happy to have me come as lab chief, I think, and shortly after that, you turned up.

IK: Even before that though, you were interested, as I remember, in adrenochrome, in the adrenochrome hypothesis of schizophrenia.

SK: Was that before you came?

IK: That was about the time I came, because Julie was sort of attracted to the path laid by you, as I remember. This was somewhere just around the time when I came. I was your first research associate and we were talking about serotonin and tryptophan at that time. My first project was to make radioactive tryptophan, but that was to follow along serotonin thing, but I think you stimulated interest also in the catecholamines because of the pink adrenaline story.

SK: Well, yes, I felt that the function of this Laboratory of Clinical Science was to attempt to bridge the gap between the basic sciences and the clinical program, and I felt that one thing that we could start with was schizophrenia. Now, I definitely did not want to assign people to work on schizophrenia, but I thought it might be possible to stimulate interest in schizophrenia by having a series of seminars at which various members were allowed to present papers, reviews or whatever on schizophrenia. And, very early in that series, I talked about some work that I'd heard about going on in Saskatchewan by Hoffer and Osmond on adrenochrome. They claimed that oxidized adrenaline injected into human beings would produce symptoms like those of schizophrenia. That was a long story. Firsts they became interested in pink adrenaline. During the war, people who got pink adrenaline, pink because it was oxidized to adrenochrome while sitting around, were claimed to have gotten hallucinations. Hoffer and Osmond became interested in pink adrenaline and injected

adrenochrome into themselves. They claimed that they had hallucinations and that it produced all kinds of symptoms. In any case, it seemed that it would be interesting to study what adrenochrome did in human beings and study its metabolism. Their theory was that in the schizophrenic adrenaline was metabolized by an erroneous pathway to adrenochrome and that adrenochrome was hallucinogenic and produced the symptoms of schizophrenia. In order to test that, we were stuck because we didn't even know the normal metabolism of adrenaline, let alone its metabolism in schizophrenia. I thought that the thing that I would like to do was to study the metabolism of adrenaline under normal circumstances and in schizophrenics. But in order to do that I knew that, it would be necessary to get radioactive adrenaline of a very high specific activity, because adrenaline is such a powerful pharmacologic agent that one could only give traces of it. So it had to be loaded with enough radioactivity to be able to measure. C^{14} adrenaline, which was available, would not be suitable. And, I tried to get one or another of the laboratories that were then working with radioactive materials to make some tritiated epinephrine. I finally got Seymour Rothschild at New England Nuclear to agree to contract from the NIMH to make tritiated epinephrine and he worked on it for a while. Interestingly enough, by the time the tritiated epinephrine came to our laboratory, Julie Axelrod had already worked out the normal metabolism of adrenaline.

IK: That was around 1957. I think it was at the Federation Meetings in Atlantic City in April of that year that Armstrong and Shaw found VMA, the major metabolite of adrenaline in the urine of patients with pheochromocytoma. Julie was in the audience and after he came back from the meeting he started to become interested in adrenaline metabolism and discovered catechol-O-methyl-transferase. But I think that the metabolism of adrenaline in animals or in patients had not yet been worked out and it was due to the tritium-labeled adrenaline that was produced under your prompting that made it possible for all these other studies to begin.

SK: Well, Julie, worked out the catechol-O-methyl-transferase and the metabolism by that route. In fact, he did the whole metabolic series that he published before the radioactive adrenaline came.

IK: That's about the time that I arrived.

SK: What the radioactive adrenaline did was to permit us to do the study in human brains. And using radioactive epinephrine, we did what I had hoped to be able to do. We administered that to normal subjects and to schizophrenics and studied what came out in the urine. Now, before Julie's contribution I thought that we would do simply chromatography the urine and look for where the

radioactivity was and see if the radioactivity appeared in spots in the schizophrenics and that it didn't appear in the others and, then, we would try to trace it down. But, when we started the work, we knew what substances to look for, how to extract.

IK: Roger McDonald set up these long columns with the assay of VMA.

SK: And, LaBrosse and Mann did the analysis of the urine and studied the radioactive metabolites in schizophrenics and normals using Julie's methods for discriminating these substances, analyzing them and so on. They eventually found that they could not find any adrenochrome in the urine of the schizophrenics and also that adrenaline disappeared in the blood of the schizophrenics at the same rate that it disappeared in the blood of normals. So, we were unable to confirm any of Hoffer and Osmond's hypotheses about adrenochrome. But, Julie went on and we also had Seymour Rothchild make radioactive noradrenaline. It was the radioactive noradrenaline that Julie used to make the discovery of reuptake, which I think was actually the discovery that won him the Nobel Prize.

IK: Right.

SK: He came to me and asked if he could have some of the radioactive noradrenaline, which I, of course, was only too happy to let him have because that's why we made it, and he said that he wanted to study its' distribution in the body of cats or rats, both. And, I said, well, you know, what do you want to do that for, that's sort of half-baked idea to study the distribution of adrenaline in the various organs. But, I gave him the stuff anyhow. He measured the distribution of radioactive norepinephrine and he found that it was highly concentrated in those structures and in those tissues that had a high density of sympathetic nerve endings.

IK: Endogenous norepinephrine, right?

SK: And, from that, he concluded that the noradrenaline, radioactive noradrenaline, he had injected, was being taken up by nerve endings and being stored in the vesicles.

IK: George Hertting was with him at the time, and Fleckenstein from Vienna where George had come from in Austria, had described the potentiation of noradrenaline by cocaine. And, if you remember, there was also Bacq in Belgium, who had reported that pyrogallol potentiated catecholamines. Together, those two findings, that pyrogallol was found to be an inhibitor of catechol-O-methyl-transferase, and that cocaine inhibited uptake, led Julie to conclude that uptake is important and that perhaps drugs influence this uptake. And, that's what started the story of the transporters, really, because cocaine was the first drug to be shown to inhibit the uptake of

noradrenaline. This was a paper that was published with George Hertting. It started a whole new avalanche of research in the catecholamine area and, again, you played a very important role in stimulating some of the hypotheses of catecholamines in relation to depression. Joe Schildkraut had come into the lab somewhat later, but I think all of the connections of biological substances with psychiatric illness grew out of the ideas that you were fostering at the time and encourage in the people that would come into our lab.

SK: I didn't have much to do with the direct studies in catecholamines and mental illness. Joe Schildkraut developed the catecholamine hypothesis entirely on his own.

IK: I don't think that would have happened if he were not in the environment that you created.

SK: Ah. He published a paper with me. He put my name on it because we had many discussions together and I felt that I.....

IK: He was right, I think, in doing that, because I don't think that would have been developed without many of the concepts of biological psychiatry that were the basis of future studies, or without other conversations with you. You helped generate the general concepts of the importance of drugs and biological interactions with these drugs in brain as clues to mechanisms of mental illness. You may not take responsibility for these things, but if they had been bad they would have been blamed on you anyway, so you may as well take credit that you really deserve for some of the things.

SK: I remember making a big point about the chemical neurotransmitters. I was fascinated by these chemical synaptic transmissions, which was a new concept then.

IK: We skipped one thing, though, chronologically. Somewhere around 1960, you, largely in recognition of the importance of biological psychiatry and your critical role in it, were offered and accepted, for at least for a short time, the position of chairman of the department of psychiatry at Johns Hopkins. And, this was really a departure from the traditional appointment of a chairman of psychiatry, because I don't think that you were a psychiatrist although I understood it from Josie, that there was a time where you underwent psychoanalysis. Can you tell us about that? I remember a very amusing conversation that you had with her with regard to the offer of the NIH to pay for your psychoanalysis.

SK: Seymour Vestermark, a blessed memory, was head of training in the early Mental Health Institute and right after I was appointed a scientific director, he came to me and said, "Seymour, I

think you ought to have a psychoanalysis and we'll pay for it, because the scientific director of the Mental Health Institute ought to know something about psychoanalysis". So, I came home and I told Josephine that they wanted to give me a free psychoanalysis and she said, "If they offered to take your appendix out for nothing, would you let them do it"? So, that was enough for me to come back and tell Seymour I wasn't interested. So, he didn't come back again until about 1960, when again he broached the subject and by this time I thought, well.....

IK: Have your appendix out.

SK: I thought I'd have my appendix out for nothing. And, so, they picked the dean of psychoanalysts in Washington, Edith Weigart, a lovely woman from Vienna, and I went through about a year of psychoanalysis, at which time....

IK: You qualified for being chairman of the department.

SK: In the middle of that, I was offered the chairmanship of psychiatry at Hopkins, which was the most distinguished chair of psychiatry in America, because it was the chair that Adolph Meyer had established and he was the father of American psychiatry. And, I was struggling with whether to accept that position while I was in analysis and I think I spent most of the time in analysis arguing with myself as to whether to take that job or not. And, I remember getting angry with Edith, because I would say, "You know more about me than anybody else. What do you think I ought to do? Why don't you ever give me any advice? Why do you let me make all the decisions and let me struggle with these decisions entirely on my own"? Well, finally, I accepted and the reason I was offered the position was that the search committee at Hopkins decided that the time was ripe for a biologist to be chairman of psychiatry and they didn't care whether I was a psychiatrist or not. In fact, I wasn't a psychiatrist. I was a physiologist. And, so, I went to Hopkins for a year.

IK: And, about that time, that's when the ACNP started.

SK: Yes.

IK: Can you tell us about your role in starting the ACNP?

SK: I was a charter member and Paul Hoch was a good friend of mine and also Fritz Freyhan. I had worked with Fritz. In fact, with Fritz, we had done the studies of the cerebral blood flow in schizophrenia. And, Paul Hoch was the one who started the ACNP and he gathered around him a group of people, including me, and I was member then of the first Council. Joel Elkes, by that time, had come to the NIH. That was all I did with regard to the ACNP. I was a member of the Council.

IK: The time had become so ripe for having a college of this nature because of the interest in biological psychiatry and also because of the rise of some psychopharmacological agents. I think that the founders of this college really were following up on many of the ideas that were current then and which you had such a major role in developing; the importance of bridging the basic science in pharmacology and in neurochemistry with brain function and mental disorders. I think that was probably why you were included in the group. I'm sure it was.

SK: I was one of the few people around doing biological studies in psychiatry or fostering biological study of psychiatry.

IK: What happened when you came in and sat on the chair, Adolph Meyers' chair?

SK: All these very important things I remember! Sitting down on Adolph Meyers' chair and the chair promptly fell down and we decided that the chair of psychiatry of Adolph's, the chair of psychiatry had to be repaired, so we called the maintenance department and had the chair repaired.

IK: I see. Well, did all that repair entail your returning to NIH, because a year later you did?

SK: Well, I discovered that I really wasn't interested in being chairman of the department of psychiatry because being chairman of any department is not the great pleasure nowadays. With psychiatry, it's even worse, because with psychiatry, you deal not only with administrative matters that have to do with medicine and research, but you deal with administrative matters that have to do with nurses and police and social workers and a whole *mélange* of health professionals and I had very little interest in that. I didn't mind administering research, but administering more than that was not of great interest. So, after a year of that, I screwed up my courage and went to see the dean at Hopkins and told him that I was sorry to say that I would like to relinquish the position.

IK: Then, you came back to NIH for a few years. Then, you went, for a year, to Paris and then we didn't see you again for a long time.

SK: I didn't go to Paris until '67.

IK: That's right, but that was a number of years later, but you did not come back to NIH from Paris. You went to Harvard and you, I think, developed the Mailman Research Center at McLean Hospital. Later, we were fortunate enough to attract you back to NIH. I'm not sure how that happened, but that was a good thing for us, certainly, and you've continued there as a senior scientist, influencing, continuing to influence the cause of research and that seems sort of full circle, because people are doing a lot of the things that you set out to do when you were doing your early cerebral blood flow,

the metabolism of the brain and how it changes. Now, we use the new imaging techniques that Sokoloff developed out of much of the work that you did. He is attending many of the ACNP meetings and we see imaging as part of all of this process of understanding how the brain works. All that is really an outgrowth of work way back when you started studies of cerebral metabolism and the biological psychiatry you fostered has grown. I think that we've used up about our allotted time.

There's so much more that we could continue to talk about because you've had such a distinguished career and you've influenced so many people. Fully, one half of the college is descended from the people that you've trained, either directly or indirectly as grandchildren and great grandchildren of the trainees that came through the Laboratory of Clinical Science.

SK: Well, we've managed to talk about, we've spent a lot of time talking about what you think my contributions were to biological psychiatry and to pharmacology, but we haven't talked about the studies that had really little to do with pharmacology, namely, the use of the adopting strategy, the study of the genetics of schizophrenia, and also the blood flow, the regional blood flow studies which I did shortly after I came to NIH. While I was still scientific director, Bill Landau came to see me from Wade Marshall's laboratory and he thought it would be nice to measure regional cerebral blood flow and he asked if he could work with me in doing that.

IK: You had all those equations worked out already.

SK: I said, "You came to the right person, because I have the equations that I've just been dying to try out but haven't had a chance to do it, and if you're interested, we can get together and try to apply those equations to the study. And, so, Bill Landau got Walter Freygang to join him and Lou Sokoloff by that time had come down to NIH and I asked him to join us in that. Bud Rowland, who was also a post-doc in Wade Marshall's lab, joined us and the four of us spent a good year or two developing the regional blood flow studies using those equations and using a band-saw to cut up the frozen brains of cats, which were loaded with a radioactive inert gas, trifluoriodomethane and making autoradiograms. These were the first regional blood flow studies, studies of the regional circulation of the brain. Bill Landau, then published a paper, with all of us, giving twenty-eight regions of the brain and measuring the cerebral blood flow in those regions. And, that was the technique which was eventually picked up by Marcus Raichle and used in the positron emission tomography, using radioactive water in his studies of regional blood flow in the human brain. Lou Sokoloff took off from that and went further. It had been my hope that, eventually, once we

measured regional blood flow it would be possible to measure regional oxygen consumption. But Lou decided that regional glucose metabolism was going to be easier to measure than oxygen consumption and developed, entirely on his own with Martin Reivich, the deoxyglucose technique. It was the deoxyglucose technique that I think first established a *raison d'être* for the PET scanners, which then became the first instrument for measuring blood flow and metabolism in human brain.

IK: I don't think we have too much time left, but tell us a little bit about the genetics of schizophrenia, because that was a landmark study and, again, it's the beginnings of the genetics of mental disorders.

SK: Well, in '59, I wrote a review for *Science*, on the Biochemical Theories of Schizophrenia, in which I reviewed papers that had been published purporting to show a biochemical lesion or a biochemical fault in schizophrenia. I discovered, to my disappointment, that most of these theories did not hold water and they were based on poor techniques and poor controls and, then, a lack of replication and so forth. But, the one area that seemed the most promising was the evidence that genetic factors play a role in schizophrenia. And, what was the evidence? Well, schizophrenia runs in families, but that had not really disturbed psychiatrists very much because they agreed that it ran in families, but the reason that it ran in families was because parents had taught it to their children. And, so, the schizophrenogenic mother and schizophrenogenic parents hypothesis flourished under the familial distribution of schizophrenia. Then, there were the twin studies and there were a number of twin studies in which high concordance rate was found in monozygotic twins and lower concordance equal to that in siblings found in fraternal twins. But, even that didn't shake the psychogenic theories of schizophrenia because they argued that monozygotic twins share a lot of their environment, much more than dizygotic twins do and one couldn't be sure that it was genetic factors rather than environmental factors. But, it was then that I thought that there was a way of separating the environmental from the genetic factors in a better way than had been done and that would be the study of adopted people, adopted individuals who had developed schizophrenia. In order to do this, I decided that one would need a national study and I wrote this in that review that I published in '59. I laid out the strategy that one could use for studying the distribution of schizophrenia in the biological and the adoptive families of adopted schizophrenics and pointed out that it would require a national sample and that efforts would have to be made to minimize subjective bias and ascertaining bias and so on. And, I discovered, then, that David Rosenthal at

NIMH was interested in doing an adoption study of schizophrenia, that he was interested in studying the children of schizophrenic parents and how they grew up and developed schizophrenia. Paul Wender was not only interested in doing an adoption study, but actually started to collect a sample population. His interest was in the adoptive parents of schizophrenics to see to what extent the schizophrenia in these people could possibly be attributed to the adoptive parents. And, he was pulling together a sample of adoptive parents but not having a great deal of ease doing this in America. We learned about Denmark, which had wonderful records, population records and psychiatric records and a national psychiatric register and, so, in 1963, I flew over to Copenhagen and met with Fini Schulsinger, who introduced me to the records that they have there. With our assurances of complete confidentiality, they made those records available to us and we set up a national register of all the adopted people in Denmark, who had grown up. In that register, we found those who had developed schizophrenia. Then we were able to trace their biological relatives and their adopted relatives and find out if schizophrenia runs in families, which family of an adopted schizophrenic does it run in, the biological family or the adopted family and we found that it ran in the biological families.

IK: Well, it's really been great for you to review with us some of the early history of your career and a little bit about the impact that it had on biological psychiatry, which is really what the ACNP is all about. So, thank you very much. It's been a real pleasure for me to be able to review with you some of these things, most of which I didn't know, some of which I did know.

SK: You cut me off before I was going to talk about your coming into the laboratory.

IK: We're not here to talk about me. We're here to talk about you.