

## SEYMOUR S. KETY

Interviewed by Irwin J. Kopin

San Juan, Puerto Rico, December 12, 1995

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 National Institutes of Health (NIH), first as the scientific director of what was then precursor of two different institutes, called the National Institute of Mental Health (NIMH), which at that time included the National Institute of Neurological Diseases and Blindness (NINDB), among other things. Somewhere around 1956, he stepped down from his post as scientific director, 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 and many members of the National Academy of Sciences, and was the spawning ground of at least half the psychiatrists in the United States 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, if not in the world, and it's indeed a pleasure to have an opportunity to elicit some of his early memories of his science and the major contributions he's made over these many years.

Seymour, can you tell us how you got started from your early years, during internship and research on lead poisoning; how did that lead to your later research? You went to Boston with this background, but soon you returned to the University of Pennsylvania; tell us about that.

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\* Seymour S. Kety was born in Philadelphia, Pennsylvania in 1915. Kety died in 2000.

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 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. 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 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 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 studies in the laboratory there and one of the studies I concentrated on was an examination of the lead citrate complex. I published my first paper in the *Journal of Biological Chemistry*, which was a characterization of the lead citrate complex. Later, Letonoff and I administered sodium citrate to patients at the hospital who were suffering from lead poisoning. Letonoff was measuring lead in the urine and lead blood levels and found that sodium citrate did have a therapeutic effect. That was the first treatment of lead poisoning with a chelating agent. Shortly after, much more powerful chelating agents were developed and lead poisoning has been treated with these ever since. As a result of that lead study and my interest in lead poisoning, I applied for a National Research Council (NRC) fellowship to work with Dr. 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 World War II.

IK: This was about 1940?

SK: I went to Aub's laboratory from 1942 to 1943. That was before America got into the war, but the war was imminent, and I had attempted to enlist in the Medical Corps, but the army rejected me because of an old fracture I had with some infection of the bone. Dr. Aub's laboratory was working on shock, not on lead poisoning, so I participated in that. There was another postdoc in Dr. Aub's laboratory, Alfred Pope. He and I were the two low men on the totem pole and spent many evenings together taking care of dogs in shock, measuring their blood pressure regularly and so on.

IK: That must have been a rough year for you, because you were married and 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 1941, becoming an intern at Philadelphia General Hospital, as was I. 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 evenings 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 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 cerebral blood flow in the rhesus monkey by using an ingenious bubble flow meter, which had been developed by Rachmiel Levine. These were the first reliable quantitative measurements of cerebral blood flow, at least in lower animals.

I decided I would be returning to Philadelphia at the end of my fellowship. I had written to Carl Schmidt and asked whether I could work in his laboratory. He offered me a position, and I worked with him on the metabolism of the brain of the monkey, using the bubble flow meter. But we also measured arteriovenous (AV) 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 the possibility of studying 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 and insights; it's the human brain that can speak and reveal its inner workings.

IK: At the time there were 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.

SK: 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 tap an artery to get arterial blood, they could measure the AV 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 examining the AV oxygen difference and using the Fick equation, which states that blood flow through an organ is equal to the amount of oxygen taken up by that organ, divided by the AV oxygen difference. 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 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.

SK: Himwich was interested in metabolism rather than blood flow, because he was studying mental retardation and other mental disorders. He used the AV difference as a measure of the oxygen consumption with the assumption that the

- blood flow is constant. The difficulty with both these techniques is that the AV difference is the result of both oxygen consumption and blood flow to the brain.
- 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 anesthetics?
- SK: By and large, they guessed right. Although they weren't able to make absolute measurements, they would make qualitative measurements.
- IK: What was the conclusion they reached with anesthetics?
- SK: Well, they made some false assumptions. With 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. By and large, they guessed right. But 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 the very state one is studying, the oxygen consumption may vary. And so, I thought, why not use a gas that, unlike oxygen, isn't metabolized? The amount of gas that would be taken up would be the result of purely physical properties like the solubility of the gas in brain tissue, the principles of diffusion from capillary into tissue. These factors could be independent of whether the brain was thinking or sleeping or suffering from one or another disease that didn't seriously affect the solubility of a gas in the brain. When I was in Boston, I'd attended a number of "shock dinners" that people in Boston working on shock used to have, including all the staff of Dr. Aub's laboratory. We would invite outside speakers to the dinners, and these lectures were supported by the Macy Foundation. On one of these occasions, André Cournand came to Boston to 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 he was studying physiological parameters in human veins, and measuring them more reliably and more accurately than had ever been done in animals by using an indirect technique which was minimally invasive; certainly not as invasive as the surgery that was required in most animal studies. That convinced me it was possible to study these physiological processes in human subjects, 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, 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 I was proficient, I approached a patient in the neurology building, who had been in that building for years and was happy to find a physician interested in talking to and studying her.

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

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

IK: The pair being the arterial and the venous?

SK: Right. Now, with those two curves, it was simple enough to get the AV difference, but the difference was not constant as it would be with oxygen. It was a variable, because the brain eventually came to equilibrium with nitrous oxide at the tension in arterial blood. The AV difference started wide, and then gradually narrowed as it went along. So, one could integrate the AV difference and get the

amount of nitrous oxide taken up by the brain. 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 equilibrium or close to equilibrium with the blood exiting it, which turned out to be about ten minutes on the basis of calculation and studies in dogs, the venous blood emerging from the brain was in practical equilibrium with the brain tissue itself.

IK: The 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 with 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. That's why the blood flow emerged in milliliters per hundred grams per minute. I then explained this to Carl Schmidt, showed him the curve and told him 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. 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 wartime. We published the values in these normal young men for cerebral blood flow and oxygen consumption.

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

SK: We didn't do glucose utilization at first, but we did it shortly afterwards in normal controls. With the glucose utilization and 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 dim compared to the huge amount of energy necessary to feed computers at that time. Of course, since 1942 or 1943, computers have become miniaturized and the energy utilized by them is much less. I suppose it won't be very long before computers will be developed that utilize 20 watts of energy and perform the kinds of functions that the human brain is capable of.

IK: How did you come to NIH? This was one phase of your career, a time when you were getting interested in 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 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 you published on diffusion of gases, which has really been a classic?

SK: No, Julius didn't make any pretense of being a mathematician. 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. I wrote that review because Goodman and Gilman, who were editors of *Pharmacologic Reviews*, asked me to write a review on the exchange of inert gas between blood and tissue, and I thought that was interesting, something I wanted to do anyhow. 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, I calculated, in a more extended fashion, the uptake of ether by the human lungs, circulation and brain, using a much more exact replica of the situation than Haggard, who was the first person to attempt to write an equation for the uptake of ether. The equation I



came up with was more exact, and with that one could relate the speed of induction of inhaled anesthetics on the basis of their solubility in blood and of physiological parameters like ventilation and cardiac output. 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 would be of great importance to me in a few years' time. But you asked how I came to the NIH. Just about the same time 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 director of the National Institute of Mental Health, a new institute of the National Institutes of Health. He asked me if I would be interested in joining him as the scientific director of the mental health institute and we had a nice conversation. I thought he was a lovely man, and felt it was going to be difficult for me to turn him down because he was such a generous person, but I knew I wasn't going to work for the government. I was perfectly happy in academia, working at the university with Julius Comroe. But he urged me to visit the National Institutes of Health, and so I went there. With Josephine and Bob Felix he showed me the Clinical Center, which was still in the construction stage, walked me through the laboratories 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 the world had ever seen. Those 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 met with the people at the mental health institute, John Eberhart and others who were working with Bob Felix in the new institute, which hardly had a place where they could do administrative work, and I also 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, with Harry Eagle and a number of the other scientific directors. Somehow I became convinced this was a challenge and an opportunity 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 later

became the National Institute for Neurological Disorders and Blindness. I was 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 became interested in talking to me because of the nitrous oxide technique and because I had collaborated on a study of schizophrenia, which was published in the *American Journal of Psychiatry*. Bob, with a little prompting by the directors of the NIH, decided it would be a good idea to have a scientist as Director of the NIMH and since the neurology institute was to be part of the affiliation it would also be good to get somebody interested in biology. And when he saw the paper on cerebral blood flow in schizophrenia, he thought I was his man. So I moved in 1951.

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

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

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

SK: That was a very exciting list. The first laboratory I set up – having said all this about biology – was the Laboratory of Socio-Environmental Studies. I set that up because that was the field I knew least about, and because I wanted to make sure we didn't forget about the extra-biological factors that determine mental illness. I sought a director for that laboratory and found we had an outstanding sociologist already working with Bob Felix at the NIMH, and that was John Clausen. So I made John 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 laid the groundwork for studies of the motor and sensory cerebral cortex, which he eventually pursued with Rose and Bard at Johns Hopkins. Then Wade became seriously ill and left the project while Rose and Bard went on to pursue it. They made beautiful maps of the cortex of the cat and monkey, which was followed by studies of the human cortex by the neurosurgical group in Montreal. By the time I got to the NIMH, Wade Marshall had been discharged from hospital, had taken a job with Bob Felix in neurophysiology, and was also doing very nice work on the cerebral cortex.

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

SK: Well chlorpromazine was introduced in the United States around 1952 or 1953.

IK: Right.

SK: In 1951 it was being studied in France. Wade Marshall turned out to be an excellent chief of neurophysiology 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 as head of a Laboratory of Comparative Pharmacology, and he brought Seymour Kaufman into his laboratory. When I appointed these people, the understanding was they did not have to work on mental illness. They didn't have to promise to work on the brain. They were to work 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 recruited Sandy Palay as one of his section chiefs. Palay became an outstanding electron microscopist of the brain.

Alex Rich came from Linus Pauling's laboratory to see me about a position at the NIMH, and Alex impressed talking about the macromolecules of the brain, how protein synthesis might be taking place and how the proteins might be responsible for encoding memory. And I had a long conversation with Linus Pauling on one of his trips to Washington; I remember sitting on a park bench outside the hotel where Linus was staying, and getting his generous recommendation of Alex. So Alex came in as chief of a Laboratory of Physical Chemistry and brought into that laboratory a number of outstanding molecular biologists, who 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 asked if there was an opportunity to join the mental health institute, and thought that he would like to work in Dr. Cantoni's laboratory, because Cantoni was 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 and their metabolism but these were not areas 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, a psychiatrist and psychoanalyst from Chestnut Lodge, who was developing the clinical program, which was largely non-biological. I thought it would be a good idea if Bob were to have a laboratory on the clinical side, interested in biology. Bob had already started such a laboratory with Marion Keyes and Ed Evarts, and was also working with Wade Marshall at the time. So I called Steve Brodie to make sure he knew I was thinking of offering Axelrod a position. We didn't want to rob another institute without letting them know.

IK: Julie had just obtained his PhD hadn't he?

SK: No, he hadn't. I referred Julie, then, to Bob Cohen saying he looked like an extremely attractive individual and it would be good if he gave him an

appointment in the laboratory he was developing on the clinical side. So Julie joined the NIMH working in that program. By that time, I had asked Lou Sokoloff, who had been working with me at Penn, to join me at NIH. 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 to do some research in addition to organizing the Intramural Program. In 1956, I felt 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 the position of scientific director to become a laboratory chief. Bob was very generous; he saw the possibilities, and permitted me to step down. I became chief of a new laboratory, which had already been started with Ed Evarts, Julie Axelrod, Marion Keyes and Roger McDonald, then nominally the chief. He had decided to call it the Laboratory of Clinical Science. They were all happy to have me as lab chief and shortly after that you turned up.

IK: Even before that you were interested in the adrenochrome hypothesis of schizophrenia.

SK: Was that before you came?

IK: That was about the time I came, because Julie was attracted to the path laid by you. 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, to follow along the serotonin line; but I think you also stimulated interest in the catecholamines because of the pink adrenaline story.

SK: Yes, I felt the function of this Laboratory of Clinical Science was to attempt to bridge the gap between basic science and the clinical program, and one thing 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 presented papers, reviews or whatever on the topic. Very early in that series, I talked about work I'd heard about 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. First

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 hallucinations. Hoffer and Osmond became interested in pink adrenaline and injected adrenochrome into themselves. They claimed they had hallucinations and that it produced all kinds of symptoms. In any case, it seemed it would be interesting to see what adrenochrome did in humans 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 the thing to do was study the metabolism of adrenaline under normal circumstances and in schizophrenics. But in order to do that I knew 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 measure. C<sup>14</sup> adrenaline, which was available, would not be suitable. I tried to get one or another of the laboratories working with radioactive materials to make some tritiated epinephrine. I finally got Seymour Rothschild at New England Nuclear to agree to a 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 vanillylmandelic acid (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-methyltransferase. But I think the metabolism of adrenaline in animals or patients had not yet been worked out, and it was due to the tritium-labeled adrenaline produced under your prompting that made it possible for these other studies to begin.

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

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

SK: What the radioactive adrenaline did was permit us to do the study in human brains. And using radioactive epinephrine, we did what I had hoped. We administered it to normal subjects and schizophrenics and studied what came out in the urine. Now, before Julie's contribution I thought that we would simply do chromatography of the urine and look for where the radioactivity was and see if the radioactivity appeared in spots in schizophrenics where it didn't appear in normals, and then try to track it down. But, when we started the work we knew what substances to look for and how to extract them.

IK: Roger McDonald set up these long columns for 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 and analyzing them. They eventually found they could not identify any adrenochrome in the urine of the schizophrenics and also that adrenaline disappeared in the blood of the schizophrenics at the same rate it disappeared in 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 Rothschild make radioactive noradrenaline. It was the radioactive noradrenaline that Julie used to make the discovery of reuptake, which I think was the discovery that won him the Nobel Prize.

IK: Right.

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

- IK: Endogenous norepinephrine, right?
- SK: From that he concluded that the radioactive noradrenaline he had injected, was being taken up by nerve endings and 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 there was also Bacq in Belgium, who reported that pyrogallol potentiated catecholamines. Those two findings, that pyrogallol was an inhibitor of catechol-O-methyltransferase, and cocaine inhibited uptake, led Julie to conclude that uptake is important and that perhaps drugs influence the uptake. And that's what started the story of transporters, because cocaine was the first drug to be shown to inhibit the uptake of noradrenaline. This was a paper published with George Hertting. It started an avalanche of research in the catecholamine area, and you played a very important role in stimulating the hypotheses of catecholamines in relation to depression. Joe Schildkraut had come into the lab somewhat later, but all the connections of biological substances with psychiatric illness grew out of the ideas you were fostering at the time and encouraged in the people who came into our lab.
- SK: I didn't have much to do with the direct studies on 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 you created.
- SK: He published a paper and put my name on it because we had many discussions together.
- IK: He was right in doing that, because I don't think the theory would have developed without many of the concepts in biological psychiatry that were the basis of future studies, or without conversations with you. You helped generate the general concepts of the importance of biological interactions with drugs in brain as clues to mechanisms of mental illness. You may not take responsibility for these ideas, but if they had been bad you would have been blamed anyway, so you may as well take the credit you deserve.



- SK: I remember making a big point about chemical neurotransmitters. I was fascinated by these chemical synaptic transmissions, which was a new concept then.
- IK: We skipped one thing chronologically. Somewhere around 1960, largely in recognition of the importance of biological psychiatry and your critical role in it, you were offered and accepted, at least for a short time, the position of chairman of the department of psychiatry at Johns Hopkins. This was really a departure from the traditional appointment because I don't think you were a psychiatrist, although I understood from Josie that there was a time when you underwent psychoanalysis. Can you tell us about that? I remember a very amusing conversation you had with her in regard to an offer by the NIH to pay for your psychoanalysis.
- SK: Seymour Vestermark, of 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 an analysis and we'll pay for it, because the scientific director of the NIMH ought to know something about psychoanalysis." I came home and 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?" That was enough for me to tell Seymour I wasn't interested. He didn't come back again until about 1960, when again he broached the subject, and this time I thought, well . . .
- IK: Have your appendix out!
- SK: I thought I'd have my appendix out for nothing. 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 chairman of the department.
- SK: Yes, in the middle of that I was offered the chairmanship of psychiatry at Hopkins, which was the most distinguished chair of psychiatry in America; it was the chair Adolf Meyer established and he was the father of American psychiatry. 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 the job or not. 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 struggle with these decisions entirely on my own?” Finally, I accepted, and the reason I was offered the position was that the search committee at Hopkins decided the time was ripe for a biologist to be chairman of psychiatry and 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: About that time was when the American College of Neuropsychopharmacology (ACNP) started.
- SK: Yes.
- IK: Can you tell us about your role in starting the ACNP?
- SK: I was a charter member, Paul Hoch was a good friend of mine and also Fritz Freyhan. I had worked with Fritz; we had done studies of cerebral blood flow in schizophrenia. Paul Hoch was the one who started the ACNP, and he gathered around him a group of people, including me, and I was a member 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 was ripe to have a College of this nature because of the interest in biological psychiatry and the discovery of the first psychopharmacological agents. I think the founders of the College were following up on many of the ideas which you had a major role in developing; the importance bridging the basic sciences of pharmacology and neurochemistry with brain function and mental disorders. 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 that approach.
- IK: What happened when you sat in Adolf Meyer’s chair?
- SK: The chair promptly fell down! We decided that Adolf’s chair of psychiatry had to be repaired, so we called the maintenance department and had it repaired.
- IK: I see. Did that repair entail your returning to NIH? Because a year later you did.
- SK: I discovered I really wasn’t interested in being chairman of the department of psychiatry, because being chairman of any department is not a great pleasure

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

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

SK: I didn't go to Paris until 1967.

IK: That's right, that was a number of years later. But you did not come back to NIH from Paris. You went to Harvard, and 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 it was certainly a good thing for us. You've continued as a senior scientist, influencing research and that seems sort of full circle, because people are doing a lot of the things you set out to do when you were doing your early cerebral blood flow research, studying 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 you did. He attends many of the ACNP meetings, and we see imaging as part of understanding how the brain works. All that is really an outgrowth of work 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 we could talk about because you've had such a distinguished career and influenced so many people. Fully one half of the College is descended from people 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 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 really had little to do with pharmacology, namely the use of the adoption strategy, the study of the genetics of schizophrenia, and also 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, thought it would be nice to measure regional cerebral blood flow and asked if he could work with me 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 been dying to try out but haven't had the chance; if you're interested, we can try to apply them to our study. Bill Landau got Walter Freygang to join him, and Lou Sokoloff by that time had come to NIH so I asked him to join us. Bud Rowland, who was a postdoc in Wade Marshall's lab also joined us, and the four of us spent a good year or two developing the regional blood flow studies using those equations and a band-saw to cut up the frozen brains of cats, which were loaded with a radioactive inert gas, trifluoroiodomethane, to make autoradiograms. These were the first studies of the regional circulation of the brain. Bill Landau then published a paper with all of us, measuring the cerebral blood flow in twenty eight regions of the brain. That was the technique which was eventually picked up by Marcus Raichle in positron emission tomography, using radioactive water in 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 and developed, with Martin Reivich, the deoxyglucose technique. It was the deoxyglucose technique that first established a *raison d'être* for the positron emission tomography (PET) scanners, which then became the first instrument for measuring blood flow and metabolism in the 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 the beginning of the genetics of mental disorders.

SK: In 1959, I wrote a review for *Science*, on the biochemical theories of schizophrenia, in which I reviewed research 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 were based on poor techniques and poor controls, with a lack of replication. But the one area that seemed the most promising was the evidence that genetic factors play a role in schizophrenia. What was the evidence? Well, schizophrenia runs in families, but that had not really disturbed psychiatrists very much because they agreed the reason it ran in families was because parents taught it to their children. And so, the schizophrenogenic mother and schizophrenogenic parent hypothesis flourished to explain the familial distribution of schizophrenia. Then there were the twin studies, and there were a number of twin studies in which high concordance rates were found in monozygotic twins with lower concordance equal to that found in fraternal twins. But even that didn't shake the psychogenic theories of schizophrenia, because they argued that monozygotic twins share their environment much more than dizygotic twins, and one couldn't be sure it was genetic rather than environmental factors. It was then I thought there was a better way of separating the environmental from the genetic factors and that would be the study of adopted individuals who developed schizophrenia. In order to do this, I decided that one would need a national study and I suggested this in the review I published in 1959. I laid out the strategy one could use for studying the distribution of schizophrenia in the biological and the adoptive families of adopted schizophrenics, and pointed out it would require a national sample and that effort would have to be made to minimize subjective bias. I then discovered that David Rosenthal at NIMH was interested in doing an adoption study of the children of schizophrenic parents and how they 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. He was pulling together a sample of adoptive parents but he was not having a great deal of luck doing this in America. We learned about Denmark, which had wonderful 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

they have. 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, and which family of an adopted schizophrenic it runs 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 about the impact it has 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 these things, most of which I didn't know, some of which I did.

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.