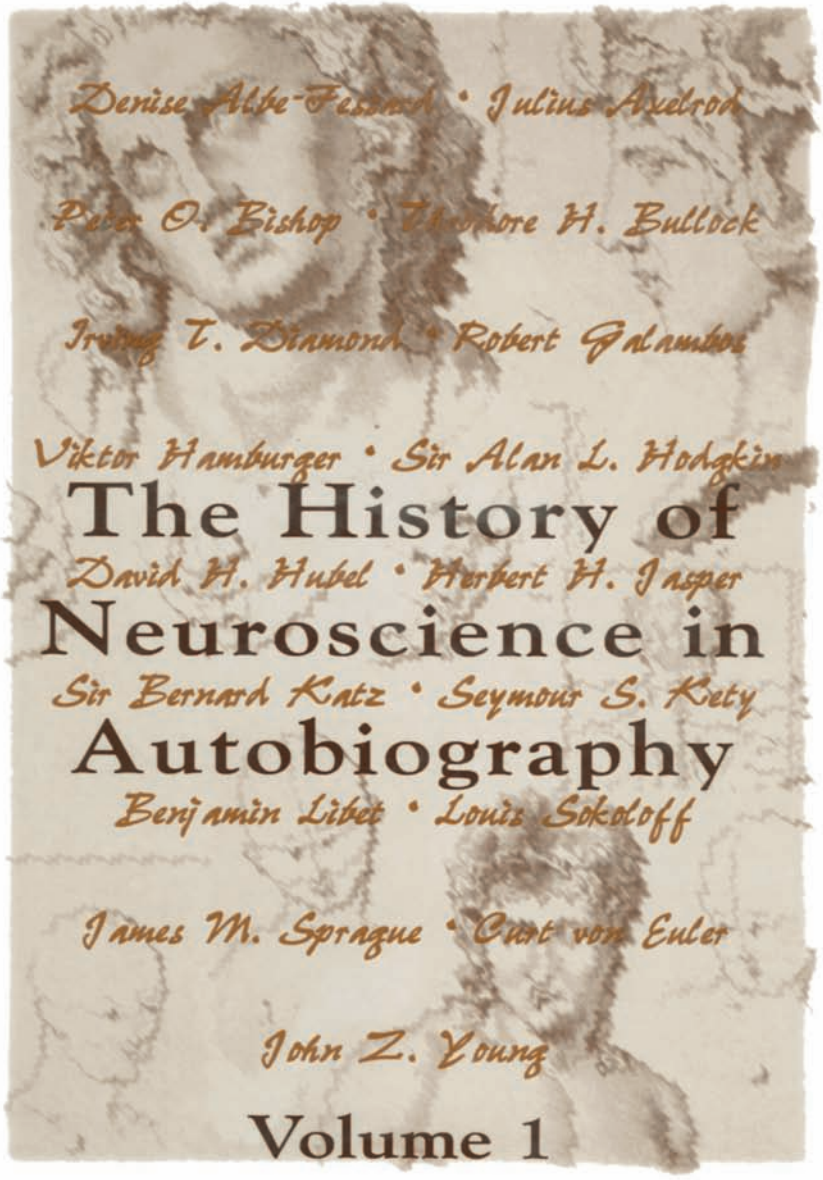


Edited by Larry R. Squire

# The History of Neuroscience in Autobiography

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# Contents

# *Seymour S. Kety*

**BORN:**

Philadelphia, Pennsylvania
August 25, 1915

**EDUCATION:**

University of Pennsylvania, A.B., 1936
University of Pennsylvania, M.D., 1940
Philadelphia General Hospital, Internship, 1940

**APPOINTMENTS:**

University of Pennsylvania (1943)
National Institute of Mental Health and Neurological Diseases (Scientific Director, 1951)
Laboratory of Clinical Science, NIMH (Chief, 1956)
Harvard Medical School (1967)
Professor Emeritus, Harvard Medical School; Senior Scientist Emeritus, NIMH (1983)

**HONORS AND AWARDS (SELECTED):**

American Academy of Arts and Sciences (1960)
National Academy of Sciences USA (1962)
National Academy of Sciences Kovalenko Award (1973)
American Philosophical Society (1977)
Passano Award (1980)
Ralph W. Gerard Prize, Society for Neuroscience (1986)
The Georg Charles de Hevesy Nuclear Medice Pioneer Award (1988)
National Academy of Sciences Award in Neuroscience (1988)
Karl Lashley Award, American Philosophical Society (1992)
Lifetime Achievement Award, International Society for Psychiatric Genetics (1993)

*Seymour Kety is best known for his pioneering studies of global and regional cerebral blood flow and oxygen consumption in the human brain. He conducted this work in normal subjects at various stages of the sleep-wake cycle and in patients with a wide variety of diseases. He also initiated the best controlled studies to date showing a strong genetic component in the etiology of schizophrenia.*

# Seymour S. Kety

I was born on August 25, 1915 and reared and educated in Philadelphia. By the time I reached adolescence, I had experienced a number of environmental influences that Anne Roe found with unusual frequency in her classical studies of the lives of biological and natural scientists. I was the first born and, for my first 10 years, the only child. My father died when I was 12 and my mother's brother and four sisters generously shared their home with us. It was a traditional Jewish home, not particularly observant religiously, but steeped in American-Jewish culture. Although financial problems were present, so were books, great music, and lively discussion. Our name was Kitei in Russia but when my grandfather came to America, an immigration officer anglicized it to Kety. In Russian Kitei means "Chinese" and there are several humorous and romantic attempts to explain the origin.

At the age of seven, I was run down by an automobile which struck my face and fractured a leg. I must have clamped down on my tongue and almost completely severed it. I was taken to a hospital and I remember the surgeon putting a needle through my tongue and sewing it together again. I was hospitalized for a long time with a fractured leg which ended up shorter than the other, and because of some scarring of the muscles and tendons, I developed an equinus, so called because I was forced to walk on the toes. For several years I wore a special kind of shoe that was conspicuous and embarrassing. It wasn't until I was 13 or 14 that I was taken to an orthopedic surgeon who cut and lengthened the Achilles tendon in a simple operation. After several weeks of being in a cast, my foot was flat and I could wear ordinary shoes.

In that earlier long period of hospitalization and home care with my leg in traction, I developed a great interest in reading. My family had bought me the *Book of Knowledge*, a series of volumes that described in a very engaging way the contents of a large panorama of disciplines: physics, chemistry, astronomy, biology, history, philosophy, and literature. I must have read practically all of those volumes in the period during which I was confined to my home. That gave me a fantastic background that substituted for athletics and other interests I might have had. I never really appreciated baseball or football. Eventually, I played some tennis.

When I was about 10-years-old, one of my aunts gave me a chemistry set; and after playing magic with that for a while, I became interested in

the science and developed a laboratory in the basement. When I was in high school I would save my lunch money and instead of lunching on shepherd's pie, I'd eat a couple of soft pretzels for which Philadelphia was famous, and go to the chemical supply house near the school and buy more interesting chemicals and supplies than came with chemistry sets. Eventually, I built quite a formidable laboratory which strengthened my interest in chemistry. In fact, I wrote a book called *The Boys' Book of Chemistry* in which I described for a young boy the principles of chemistry and led through various historic or exciting experiments. The book, of course, was never published; it was written in a series of notebooks and I was never satisfied with it sufficiently to want to see it published. By the time I got to high school I was quite proficient in chemistry.

I went to an unusual high school, Central High, in Philadelphia which, I think, was second only to Boston Latin in terms of its age and distinction. Central High began as a city college and it still retained many of the collegiate amenities. For example, we received a baccalaureate degree when we graduated and we had professors, not teachers, who all liked to teach, and many were interesting characters. I took the classical course which included Latin and Greek. The professor of classical languages, Professor Howes, was erudite and rather liberal politically. In addition to having us recite Xenophon and Caesar and Horace and Homer, he would give us discourses on politics and living. We would select someone in the class to get Howes started by asking him a provocative question as soon as we entered his class and sat down. If we were fortunate, he would discourse on that topic and we would never have to reveal how poorly prepared we were. One day he surprised us by saying, "Well, gentlemen, who's the starter today?"

I had a number of professors there who were very important as models for me. The greatest was Bradner MacPherson, a charismatic professor of English literature and a sincere friend. I remember how terribly upset I was when I learned that he had died of pneumococcic meningitis just before the advent of the sulfonamides and penicillin. The disorder, when he contracted it, was 100 percent fatal. Today it would be a simple matter to cure.

Another important influence was Edwin Landis who was the professor of physics. Edwin Landis, incidentally, was the uncle of Eugene Landis, a distinguished physiologist who did the classical work on capillary fluid exchange at the University of Pennsylvania and became a professor of physiology at Harvard. Edwin Landis inspired a number of us. He started a science and philosophy club in which we tangled with important problems like vitalism and materialism, consciousness, and the nature of consciousness for a very illuminating and exciting experience. We found a sentence in Virgil, "Felix qui potuit rerum cognoscere causas," "Happy is he who is able to understand the causes of things." It was there that I developed a long-lasting interest in the unique experience of consciousness and how it is derived from the brain, a problem to

which I still have not found a satisfactory answer, although others appear to have, at least for them.

We also learned about the General and Special Theories of Relativity in the course of which I asked a question that Professor Landis could not answer. He suggested that I write to Albert Einstein which I did. To our intense gratification the great man sent back a splendid letter in reply, which answered the question in considerable detail. What a great scientist was he who was not too busy or important to answer the question of a high school student in another country.

My maternal uncle, Harry Snyderman, who took the place of my father during my adolescence, had a great influence on me. He was extremely scholarly, read incessantly, and built up the largest collection of books that I've ever seen in a private home. He knew more about literature than anyone I've ever met since. He was an excellent critic and an accomplished grammarian. He was also a self-taught pianist. He never learned to read music but he could always play things by ear and he was remarkable in the way he would sit down and play most anything that he heard. He had a profound influence on me even though I never developed his grasp of literature or music.

I was very successful at Central High, graduating with high honors and winning a number of awards. It was said that no one had won as many in the history of the school. Because this was not my mother's claim but came from one of the older teachers, I had no basis for denying it. I went to the University of Pennsylvania on scholarship. Some of my mentors in high school wanted me to apply to Princeton or to Harvard but I didn't see the point because even if I were able to get a scholarship to those places, I would not have been able to muster living expenses. So I chose the university in the city where I lived. My education at Central High was so full and rich that college was quite a let down. I found that there was really not much of a challenge to me. Even in chemistry, I breezed through most of it and it wasn't until we got to physical chemistry that I reached the point where I had to study.

In college I had a job with a toxicologist who was interested in lead and was a consultant to a number of lead companies. He had me do lead analyses on the urine of the workers there. I used the standard procedure, part of which was to precipitate the lead as an insoluble salt and then to redissolve it with sodium citrate, in which the citrate formed a complex ion, which is called a chelate, with lead. That was important to me because I thought that perhaps it would be possible to treat lead poisoning with citrate. That disorder is associated with the deposition of lead in the bones, which perhaps citrate could extract and permit to be excreted. I was able to test that hypothesis a few years later.

I was planning to go to graduate school for a degree in chemistry, but was persuaded instead to apply to medical school, which turned out to be a

wise choice. The preclinical years in medical school gave me a much broader education in the biological sciences, especially those of the brain which no single department of the graduate school could have provided. Neuroscience was not a course or even a discipline in 1935; was it even a word?

During a research elective at medical school, I had an opportunity to test my hypothesis of the mobilization and excretion of lead through chelation with citrate. I added lead to the diet of some rats until they became chronically intoxicated, then measured the excretion of lead after feeding them sodium citrate. The citrate profoundly increased the excretion of lead. I suppose you could call this the first scientific discovery that I made. Previously, the experiments that I did were just reproducing what others had done and described, but this time it was very exciting to see a hypothesis come true right in front of my eyes.

When I completed medical school in 1940 I married Josephine Gross who was in her last year of medical school. In all the years of our marriage she has shared my work and decisions, graciously and selflessly adapting her career to mine in the moves we decided to make. I took an internship at the Philadelphia General Hospital, the descendent of Blockley which had been the oldest hospital in the country. When Josephine was ready for an internship she chose the same hospital, not only because I was there, but because her father took his internship there in 1912. The director called me into his office to inform me that a fine female physician, who was probably my wife, was coming as an intern. Unfortunately, however, the hospital had no facilities for married couples, so I would remain in the men's quarters while my wife stayed with the female interns. Because the hospital was providing our room and board in lieu of a salary, it would have been ungrateful of me to have objected. We did manage to live together eventually. Josephine went on to residency in pediatrics and in 1990 we celebrated our 50th anniversary.

During my busy internship I spent my spare time at a laboratory studying the nature of the lead citrate ion and measuring its degree of association. I demonstrated that lead did form a very tight complex with citrate. I then calculated that there was enough citrate circulating in the blood normally to carry a significant amount of lead in the soluble complex form. This was true in chronic lead poisoning and perhaps the mechanism by which the body slowly excretes the metal. One could facilitate that process by increasing the citrate in the blood through administration of sodium citrate and thus increase the excretion of lead. I wrote this up and sent it to the *Journal of Biological Chemistry* and was very fortunate to have my first scientific paper (Kety, 1942) accepted in so prestigious a journal.

Then I administered sodium citrate to workers with lead poisoning and was fortunate to find a chemist in the hospital laboratories who was interested in lead poisoning and willing to carry out the blood and urine assays. He was able to show that citrate treatment increased the excre-

tion of lead significantly and led to a progressive fall of lead in the blood levels (Kety and Letonoff, 1943).

That was the forerunner of the chelate treatment that became the standard treatment for lead poisoning. This uses more complex organic molecules that form a much tighter complex lead.

After I completed my internship, I applied for a National Research Council fellowship. I wanted to go to Boston to work with Dr. Joseph Aub who was the world authority on lead poisoning. I was still interested in lead poisoning and, as a matter of fact, it was the work that I had done on citrate and lead poisoning that won the fellowship. I wrote to Dr. Aub and asked about coming to join him.

Shortly after joining Dr. Aub, World War II broke out. I applied for a commission in the Army, but was rejected because of residua from my accident 20 years earlier. Dr. Aub had replied with a strong welcome but with a warning that he wasn't working on lead. Instead, due to the war, he had turned his laboratory to the study of traumatic shock.

Dr. Aub was a warm and charming scientist. Besides his work on lead poisoning, his major contributions were in metabolism and, more recently, in cancer research. Working in his laboratory introduced me to Paul Zamecnik, who had just returned after a fellowship at the Carlsberg Laboratories in Copenhagen with Lindestrom-Lang, and to Alfred Pope, a contemporary, the same age as mine, but a Harvard man.

Alfred Pope and I became good friends and have remained so ever since. We were the two junior members of that laboratory, who stayed up late watching the dogs in shock, taking their blood pressure, and doing any biochemistry that had to be done. We became interested in shock and developed a recognition of the homeostatic reflexes that were operating in shock whose purpose, obviously, was to preserve the circulation of the brain and the myocardium at the expense of the circulation in other organs. Blood vessels of the brain and the heart are specially adapted so that they are not constricted by sympathetic activity. Stimulation of the sympathetic nervous system would cut down the blood flow to the kidneys and to the skin and to the viscera; but it would not cut down the blood flow to the coronaries and the brain for obvious teleological reasons.

Al and I wrote a paper that we published in the *American Heart Journal* (Kety and Pope, 1944) on the homeostatic reflexes that operate in shock and how they preserved the cerebral circulation. I also came across a paper published in the same year in the *American Journal of Physiology* by Dumke and Carl Schmidt from the University of Pennsylvania. This paper measured the circulation of the brain of the rhesus monkey with a bubble flow meter inserted into the internal carotid artery. This was the first time that anyone had been able to measure quantitatively the blood flow through the mammalian brain. I decided that when I finished my fellowship with Dr. Aub I would seek a position with Carl Schmidt and go back to Philadelphia.

I was successful in doing that even though Dr. Aub urged me to stay. Neither of us knew that I would return to Harvard 25 years later.

Shortly after I arrived at Carl Schmidt's laboratory, he invited me to assist him in the studies of oxygen consumption in the brain of the monkey. Besides obtaining values for that function in the mammalian brain under light anesthesia, that study also demonstrated a striking increase in metabolism during convulsions and a decrease under anesthesia (Schmidt, Kety, Pennes, 1945). Less extreme states, of course, were not readily examined. What challenged me, however, was the *human* cerebral circulation because the human brain was so different from that of the monkey even though they were very close approximations, but different as opposed to the liver or to the kidneys. The animal kidney is a very good model of the human organ, the detailed function of which can be studied and understood, one from the other. I felt that just as the brain is unique among organs for its complexity, so is the human brain unique among that of other creatures in its capacity, its versatility and plasticity, its ability to conceptualize and create, to experience ecstasy and deep grief, and to describe to outside observers the results of its inner processes. It is also the human brain that falls prey to serious disorders of these functions, for which no comparable animal models exist. It was apparent that the study of the circulation and metabolism of the human brain while it was engaged in these functions and experiences might teach us something about these processes, and its study in disease might be of benefit to those suffering from neurological or mental disorders. It was thoughts such as these that moved me to seek a means of studying the circulation of the human brain.

## Measurement of the Human Cerebral Circulation

While in Boston, I had heard an inspiring lecture by Andre Cournand, describing his early work on the output of the human heart in health and disease, and I was impressed with the possibility that clinical studies could be more physiological, relevant, and fundamental, under certain circumstances, than studies in animals. Cournand had used the classical Fick principle, calculating cardiac output (equal to blood flow through the lungs) from the oxygen taken up by the lung and the oxygen content in blood entering and leaving, all of which he could measure independently. The crucial sample was the pulmonary arterial blood which he could obtain from the right atrium by catheterization.

Much earlier, in 1927, the Boston psychiatrist Abraham Meyerson had described a simple technique for obtaining cerebral venous blood in man from the superior bulb of the internal jugular, making it possible to measure the arteriovenous difference across the brain for substances utilized or produced in significant amounts by that organ. That approach was then used by a group in Boston to infer cerebral circulation from the arteriove-

nous oxygen difference, assuming that cerebral oxygen consumption, which could not be measured, was constant. But the arteriovenous oxygen difference was also used in Albany to infer metabolic rate of the brain with the assumption that blood flow was constant. What had limited the validity and acceptance of both these approaches was that the arteriovenous oxygen difference, being a function of both blood flow and oxygen consumption, was not a valid measure of either alone. The oxygen consumption of the brain could not be measured independently and certainly could not be assumed to be constant under a wide variety of functional states, because it would be expected to vary with the state of activity or disease that was the object of investigation.

By 1943, the Fick principle had been applied by Homer Smith to the kidney, and two years later by Stanley Bradley to the measurement of hepatic blood flow. In each case they took advantage of the ability of these organs specifically to excrete a foreign substance at a rate that could be independently measured. Unlike the kidney and liver, however, the brain was not known to remove selectively and specifically a foreign substance from the blood and excrete it for accurate measurement.

I realized, however, that the brain would absorb by physical solution an inert gas, which reached it by way of the arterial blood. The accumulation of such a gas in the brain should be independent of the metabolism, determined instead by the rate of perfusion and relatively simple physical principles such as diffusion and solubility which should be quite constant in the brain whether the subject was asleep or awake, working out a complex mathematical problem or suffering from schizophrenia.

In the brain of a monkey I found that a cerebral arteriovenous difference did exist for the non-metabolized gas, nitrous oxide, as it was breathed, and that this difference went from wide to narrow over a period of 10 minutes. The Fick equation would have to be converted to differential form to deal with the nonsteady state of equilibration with a metabolically inert tracer like nitrous oxide. To solve the resulting equation for cerebral blood flow it would be necessary to measure the concentrations of the gas in arterial and mixed cerebral venous blood as the arterial blood and brain came toward equilibrium, and to integrate the difference over time.

Arterial and cerebral venous blood were obtainable but I would also need to know the amount taken up by the brain as a whole during that time. One could, of course, do this by external counting of a radioactive inert gas, but a simpler approach presented itself. The arteriovenous difference became progressively narrow with time because the brain was coming to equilibrium with the blood passing through it. If that was the case, there would be a time in which the venous blood draining the brain would be in virtual equilibrium with the brain itself and could be used as a measure of the partial pressure of gas in the brain. At that time, the cerebral venous concentration would yield the concentration of nitrous oxide in the

brain, if corrected for the differential solubilities of the gas in brain and blood. With both the numerator and the denominator measurable, cerebral blood flow in unit weight of brain (F/W) could be determined.

I could not find a flaw in this reasoning and I was now in position to explain it to Carl Schmidt. He was impressed and offered to set up some monkeys with bubble flow meters to compare my results with the meter's results in the same monkeys. He did this and the correlation between the two measures was excellent.

The equilibration between blood and brain could be studied in animals and was found to be sufficiently complete at the end of 10 minutes (Kety, Harmel, et al., 1948). It was also possible to obtain a more accurate measure of the partition coefficient of nitrous oxide between brain and blood and of the remarkably constant solubility of the gas in human brain in a variety of disorders. Later, studies with radioactive krypton indicated that in man, 10 minutes was also sufficient for nearly complete equilibrium. Two other series of studies indicated that the venous blood was well mixed by the time it emerged and that contamination from the distribution of the external carotid was minor (Shenkin, Harmel, Kety, 1948). Once cerebral blood flow could be measured, cerebral oxygen consumption could be calculated from that and the arteriovenous oxygen difference across the brain.

The first systematic study in man was carried out on 14 healthy young men who volunteered to serve as subjects (Kety and Schmidt, 1948). The values for blood flow and oxygen consumption were in the same range as those we had previously found in the monkey when both were reduced to unit weight of brain. I am still impressed, however, with how large a share of the body's economy is used in supporting the brain—about a fifth of the cardiac output and of the oxygen consumption at rest—but how small the utilization of energy by the human brain—a mere 20 watts—in comparison with what man-made giant computers required. In the 50 years that have elapsed since then, the energy requirements of computers have come down closer to that figure.

The number of problems to which the new technique could be applied were legion but I tried to select those that might contribute to fundamental knowledge about the brain, its physiological functions, or in the case of disease, where there was reason to think that an alteration in cerebral circulation or metabolism would be crucially involved. Among the very first studies was the one on schizophrenia (Kety, Woodford, et al., 1948) which was begun because it had been proposed that a deficit in oxygen supply and utilization occurred in the brain, but there was an equally cogent reason. The development of the nitrous oxide technique was supported in part by a small grant from the Scottish Rite Schizophrenia Program. Although the directors had never asked about the relevance of cerebral circulation to schizophrenia, when an application to that problem was possible we were eager to make it. This involved long trips to the Delaware State Psychiatric

Hospital with collaborators Rachel Woodford and Merel Harmel, where Fritz Freyhan, an excellent psychiatrist and investigator, had selected a series of chronic schizophrenic patients willing to participate in the studies. The results, however, were not illuminating. The brain of the schizophrenic patient had the same blood flow and utilized oxygen at the same rate as that of normal individuals. That did not dissuade me from the belief that we were dealing with a disease of the brain—the remarkable dissipation of the psychosis often produced by a chemical substance, amytal, convinced me that chemical processes were involved. It appeared quite likely that the mental changes in schizophrenia depended on chemical and neural processes too localized and differentiated to be revealed in the circulation and metabolism of the whole brain. My summary of the findings—"...a generalized change in circulation or oxygen utilization by the brain of schizophrenics may safely be ruled out, although there remains the possibility that local disturbances confined to small but important regions may still occur since the method used yields only mean values for the entire brain."—recognized the most serious limitation of the nitrous oxide technique and the need to examine the circulation and metabolism within the brain's unexplored complexities which I then proposed to address.

In respect of medical disorders, the finding that cerebral circulation was normal in essential hypertension despite a perfusing pressure that was twice normal, was important (Kety, Hafkenschie, et al., 1948). This was found without intervention by the known sympathetic supply to the brain (Harmel et al., 1948), suggesting a humoral vasoconstriction or a homeostatic autoregulation, both of which are now known to occur. Other medical or neuropsychiatric problems to which the technique was applied shortly after its development were diabetic acidosis, epilepsy, increased intracranial pressure, surgical anesthesia, and senile dementia (Kety, Polis, et al., 1950). The technique was also applied successfully to the complex problem of measuring coronary blood flow and myocardial metabolism (Bing et al., 1949).

We were not alone for long in applying this technique, in spite of its limitations, to other clinical problems. Scheinberg and Stead were the first to apply it in America, while Professor Aizawa, chairman of neurology at Keio University, introduced the nitrous oxide method in Japan, followed by Niels Lassen and his colleagues in Denmark, Cesare Fieschi and Agnoli in Italy, and several others in Europe.

In 1948, I moved to the Graduate School of Medicine, joining Julius Comroe's department of physiology, and began working on a grant I was fortunate enough to receive from the new National Heart Institute in Bethesda for studies on the theory of inert gas exchange, prompted largely by my feeling that in the exchange of inert tracers between capillaries and tissue would be found the means of measuring local blood flow in the brain. I had moved empirically in that direction in the measurement of muscle blood flow from the clearance of $^{24}Na$ ions (Kety, 1949). Now, having chosen as my next

objective the measurement and study of regional blood flow, the most promising approach appeared to lie in a more exhaustive study of the physical processes on which the nitrous oxide technique was based, that is the exchange of diffusible, nonmetabolized molecules between capillary and tissue. Louis Goodman, the editor of *Pharmacological Reviews* had invited me to write a review on the distribution of anesthetic gases and I responded by offering to review the theory of the exchange of inert gases at the lungs and tissues.

In the development of the nitrous oxide technique, the familiar Fick Principle was converted to differential form and made applicable to the accumulation of an exogenous nonmetabolized substance in the brain, rather than to the absorption of oxygen at the lungs. To solve the resulting expression for cerebral flow it was necessary to evaluate concentrations of the tracer in arterial and mixed cerebral venous blood, both of which were obtainable, but also the amount taken up by the brain as a whole, which, it was possible to show, could be obtained from the cerebral venous blood.

In the case of an individual small region, on the other hand, I saw no way of measuring the concentration of tracer in its effluent blood under physiological conditions. It would be possible, however, to measure the concentration of a radioactive tracer in the individual small regions throughout the brain by means of autoradiography in animals and external detectors in man. From the tissue concentration at a particular locus, it should be possible to derive the concentration of tracer in the venous blood from that site on the basis of physical principles. Where diffusion is not limiting, a tracer in the entering capillary blood will achieve practical equilibrium with the surrounding tissue at the time of its exit. This permitted the derivation of an expression for the concentration of tracer in a small tissue region at a specific time in terms of blood flow through the region, partition coefficient of the tracer between the tissue and blood, the diffusion constant for the tracer in tissue, the geometrical relations of the capillaries there, and the past history of the tracer in the arterial blood from the time of its introduction (Kety, 1951). In 1951, when that expression was derived, I did not foresee the many applications it would have as the technology of tracer detection and localization moved forward over the next 30 years.

There would be some diffusion limitation in the case of many possible tracers, however, and it was desirable to elucidate the physical and biological factors on which capillary:tissue equilibrium depends and to develop an expression to take them into account. Some 30 years before, Christian Bohr and August Krogh had described the exchange of oxygen at the capillaries of lung and tissue. In a steady state, oxygen gradients would be constant, but in the case of an unmetabolized tracer the gradients would change with time and introduce another level of complexity.

By building on the derivations of Bohr and Krogh it was possible to derive an expression for the exchange of an inert but diffusible tracer between flowing capillary blood and the surrounding tissue in terms of perfusion rate, the capillary diffusing surface, and the diffusion coefficient of the tracer through the capillary membrane (Kety, 1951). That derivation was a first approximation because it made two simplifying assumptions: first, that after diffusing through the capillary wall the tracer was instantly dispersed throughout the external phase, and second, that its concentration did not change there appreciably in the time of a single passage of blood through the capillary. Because the capillary volume in the brain is less than 5 percent of the parenchyma, the latter assumption would introduce a negligible error, and because the capillaries of the brain are arranged in baskets around the cellular elements rather than in parallel, the first assumption is supported by the more rapid radial diffusion.

Louis Sokoloff joined me in Julius Comroe's department as a postdoctoral fellow and in short order undertook the study of cerebral metabolism in hyperthyroid disease. We were unprepared for his finding (Sokoloff et al., 1953) that the brain did not share in the generalized increase in metabolism that occurs in hyperthyroidism. In order to explain this unprecedented result he hypothesized, and eventually demonstrated, that the important action of thyroxin was on protein rather than carbohydrate metabolism. He pursued this observation to discover the role of thyroxin on protein synthesis, explaining its effects on metamorphosis and dendritic proliferation.

We knew that in diabetic coma the cerebral oxygen consumption was reduced by 50 percent (Kety, Polis, et al., 1948), so we were not surprised to find that in deep anesthesia a similar depression in energy metabolism occurred (Wechsler et al., 1951). Our study on sleep, however, produced some surprising results (Mangold et al., 1955). Although it was not unusual for some of our subjects to fall asleep and have to be awakened during our previous studies, it was not easy to get them to sleep when we wished. I was a subject in the sleep study and although I was quite comfortable, the effort of trying to sleep kept me awake. In the course of numerous unsuccessful trials we did have six subjects sleep for the 10 minutes necessary to make a measurement. The results were unexpected. Except for one subject in which it was increased, the utilization of oxygen by the brain was mildly depressed (about 15 percent, compared to coma or anesthesia at 50 percent), in spite of the prevailing belief, which stemmed from Pavlov and Sherrington, that sleep was characterized by a suppression of neuronal activity. It was not until Edward Evarts succeeded in recording from individual cortical neurons of sleeping animals, and the confirmation provided by our later studies of regional circulation that the observations in man showing sleep to be an active process became credible.

## The Intramural Basic Research Program of NIMH

In 1950 my research was interrupted for a while by an unexpected visitor from Bethesda. The studies of cerebral blood flow in schizophrenia had come to the attention of Robert Felix, director of the newly founded National Institute of Mental Health (NIMH) in Bethesda, and in that year visited me at my office at Penn to invite me to join NIMH as its first scientific director. It was then that my commitment to psychiatric research began.

I was very happy in Comroe's department and had no desire to work for the federal government. Yet, I was challenged by the problem of mental illness, and recognized that the magnitude of the problem was matched by our ignorance about it. What greater challenge and better opportunity existed than to plan and develop a research program broad enough to examine the problem of mental illness in all of its complexities.

After thinking about it for two months, visiting Bethesda, seeing the 200 laboratories being constructed for the new institute, meeting its small but dedicated staff, and conferring with James Shannon and Harry Eagle, the scientific directors of the Heart and Cancer Institutes, I accepted the challenge and spent most of my research career there.

Dr. Felix was the ideal director for NIMH. He appreciated the need for substantially increased research and defended it valiantly. He did not presume to know in what directions our research program should go, or if he did, he did not permit that to influence me. For my part, these mysterious illnesses that had baffled the human race for centuries had not revealed any of their secrets to me.

We would need research at the clinical level, of course, but for that to be meaningful there was the greater need for considerably more fundamental knowledge in the sciences of brain and behavior to provide the foundation for rational and plausible clinical research. I could think of no better investment of the new and unprecedented resources placed at my disposal than using them to establish a broad program of basic research that represented all of the disciplines on which psychiatry depends.

Perhaps because my background was more deficient in the social sciences than in any of the others, I decided to establish the Laboratory of Socio-Environmental Studies with John Clausen as its chief. Shortly thereafter, Wade Marshall became head of neurophysiology. Alexander Rich, who appointed David Davies, represented physical chemistry—soon to become molecular biology—and Giulio Cantoni, soon joined by Seymour Kaufman, developed comparative biochemistry. When the Clinical Center was completed Robert Cohen was asked to be director of Clinical Research and together, we recruited David Shakow to direct a large laboratory of psychology, representing a wide spectrum of experimental, developmental, and clinical psychology.

I was also charged with organizing the Basic Research Program of the National Institute of Neurological Diseases and recruited several additional neuroscientists: William Windle, joined by Sanford Palay in neuroanatomy, Roscoe Brady in neurochemistry, Kenneth Cole in biophysics, Ichiji Tasaki in neurobiology, Karl Frank in neurophysiology, and Roger Sperry in developmental neurobiology, until he was wooed away by Cal Tech. One concern that some had expressed was rapidly put to rest. A government institution with the proper philosophy could attract a faculty as distinguished as that of any university (of the initial group that joined me, eight became members of the National Academy of Sciences and of the larger number we recruited and helped to train, more than 20 achieved that distinction). The research programs of the two institutes were organized in parallel and merged into a single basic research program as they should have been, since the neurosciences have as much pertinence to mental illness as to neurological disease. It is unfortunate that they were separated some years later for parochial reasons. The neurosciences, unfortunately, have continued to suffer unnecessary splits since they were recognized as a single discipline.

In 1953, I was invited to join a group of distinguished neurochemists from England (Derek Richter, Henry McIlwain, Geoffrey Harris, and Joel Elkes) and America (Jordi Folch-Pi, Heinrich Waelsch, and Louis Flexner) to initiate a series of International Neurochemical Symposia to recognize that newly articulated discipline. I had thought of myself as a physiologist rather than a biochemist, but the work on the oxygen and glucose metabolism of the human brain *in vivo* had apparently turned a new leaf in neurochemistry and made me a bona fide member. We organized a series of stimulating conferences on the cutting edges of neurochemistry, cerebral metabolism, neuropathology, and regional function, in Oxford, Aarhus, Strasbourg, and Varenna, which I am sure contributed immensely to the development of the field and led directly to the establishment of both the American and International Neurochemical Societies.

Before moving in that direction, however, several of us, but particularly Heinrich Waelsch, began talking to our counterparts in Europe, especially Albert Fessard, with the aim of forming an international brain research organization, IBRO. The nascent organization was adopted *in utero* at an International Colloquium on Electroencephalography and Clinical Neurophysiology in Marseilles in 1955. IBRO was formally organized in Moscow at another EEG and Clinical Neurophysiology Colloquium in 1958. IBRO was by no means exclusive; its first executive committee consisted of Anokhin (USSR), Fessard (France), Harris (U.K.), Magoun (U.S.), Moruzzi (Italy), and Waelsch (U.S.), with Jasper (Canada) as Executive Secretary and Waelsch as Treasurer.

The Society for Neuroscience had its roots in IBRO. A national organization of brain sciences was required to represent the United States in

IBRO and Waelsch took the initiative in setting one up. He introduced Ralph Gerard and me to the idea of establishing a Committee on Brain Sciences under the National Research Council which became our corporate member in IBRO. But the work became more than that, initiating a survey of Brain Research Resources and sponsoring historical studies of the role of basic research in important clinical advances. It was quickly realized that this committee was fulfilling a much more important need in this country than as an affiliate of a rather bureaucratic international association. The committee sponsored the new Society for Neuroscience and elected Ralph Gerard unanimously as Honorary President.

## Autoradiograms of Regional Blood Flow and Neuronal Activity

The first application of my theory and mathematical derivations of inert gas exchange at the capillary was published in 1955 with our measurement of blood flow in small regions throughout the brain of the cat (Landau, Freygang, Rowland, Sokoloff, and Kety, 1955). Shortly after I arrived in Bethesda as scientific director of the newly established Mental Health and Neurological Diseases Institutes of the National Institutes of Health (NIH), I was delighted to have a young postdoctoral fellow, William Landau, ask to work with me to examine the regional circulation of the brain. As the first and simplest approach, we selected tissue clearance, an idea that had worked very well for me in studying muscle circulation (Kety, 1949), but that was not successful in the highly heterogeneous brain. I turned to autoradiography as the technique of choice for observing and measuring the concentrations of a radioactive tracer all over the brain, which would permit us to use the equations from 1951 to compute blood flow in the various regions. We were fortunate to recruit two additional collaborators, Lewis Rowland, and Walter Freygang, from the Neurology Institute, and Louis Sokoloff who had joined me from the University of Pennsylvania. Landau and Rowland were to become two of the most distinguished professors of neurology in the United States and Sokoloff would be celebrated for developing the deoxy-glucose technique for regional cerebral metabolism.

A radioactive inert gas was used ($^{131}$I-trifluormethane) and I proposed a method for measuring its concentrations throughout the brain by means of calibrated autoradiograms from which the regional blood flow values were calculated. Because our tracer was a gas, sections were made from brains frozen in liquid nitrogen and then exposed to film at -40°. A microtome that would cut sections from frozen brain was not immediately available and my colleagues showed me that an ordinary band-saw could make excellent sections that would produce very satisfactory autoradiograms. In 1955 we published our first report of the blood perfusion in 28 structures of the living brain (although the measurements were

made on sections of the cat brain, the perfusion-determined accumulation of tracer took place in the living state). We were not surprised to find that blood flow in the cerebral cortex was four to five times as high as that in white matter, but the extremely high values in the medial geniculate and the inferior olivary nucleus challenged us. At first we hypothesized that the clicking of the radioactivity counters were activating these auditory nuclei, but when Landau completely deafened the animals the flow was not reduced. There is little doubt that the high perfusion rate reflects a high rate of functional activity in these nuclei since various respiratory enzymes have their highest concentrations there.

Among the most significant experimental observations made with the use of this technique were those on the effects of thiopental and of photic stimulation reported by Sokoloff at the International Neurochemical Symposium on Regional Neurochemistry (Kety and Elkes, 1961). Thiopental anesthesia differentially reduced blood flow in cortical regions and sub-cortical structures subserving sensory functions, while photic stimulation was associated with marked increases in perfusion of the striate cortex, lateral geniculate ganglia, and superior colliculi. Although there had been a few reports suggesting an increase in perfusion accompanying increased functional activity, Sokoloff's was the first clear demonstration of that important homeostatic relationship, and of the perceptive inference by Roy and Sherrington nearly 100 years ago that local neuronal activity, metabolic rate, and perfusion were closely coupled.

In 1961, Ingvar and Lassen were the first to apply these principles of capillary:tissue exchange of an inert gas and the derived equations to measurement of regional blood flow in man, using $^{85}Kr$, and later, $^{133}Xe$. Ingvar and Franzen were the first to study regional cerebral blood flow in schizophrenia and discovered the diminished perfusion of the frontal lobe. Weinberger has related this specifically to a deficit in cognitive function. Thus, the questions that impelled me to develop a local blood flow technique were answered in the very disorder that prompted them.

Measurement of cerebral blood flow and cerebral metabolism had usually gone hand in hand, and in 1977 Sokoloff and associates published the theory and technique for the measurement of regional glucose metabolism, using the non-oxidizable congener, 2-deoxyglucose, radioactively labeled so that its accumulation in the various regions of the brain, determined by the rate of glucose utilization, could be captured by autoradiography. The accumulation of tracer in Sokoloff's highly original technique depends not on diffusion but on chemical processes involved in transport and the spatial resolution in the autoradiograms was fine enough to delineate the ocular dominance columns of Hubel and Wiesel. The introduction of positron emission tomography (PET) which fully exploited the possibilities presented by the distribution of appropriately labeled tracers in the brain, offered an advanced and theoretically sound approach to the non-invasive mea-

surement of regional cerebral blood flow and metabolism in man. Background problems were minimal and the resolution was higher than that obtainable with earlier methods of external counting. Deoxyglucose, labeled with fluorine-18 made possible the measurement of glucose metabolism by PET in a large number of neurological and psychiatric disorders. Water labeled with the positron emitting isotope of oxygen ($^{15}O$) has been the tracer most used for blood flow although lipid soluble tracers show less diffusion limitation at high flow rates. In fruitful collaboration with Michael Posner, Marcus Raichle, using $^{15}O$ labeled water, has applied the equations and techniques for regional cerebral blood flow to human subjects performing a number of cognitive tasks. It is in the studies now possible of the neural pathways and processes involved in human thought that my early hopes regarding the measurement of human cerebral blood flow are now being realized.

Shortly after my appointment at the NIH, Seymour Vestermark, director of training at NIMH, asked whether I would like to have some experience with psychoanalysis which he thought would be only reasonable for the scientific director of a mental health institute. He indicated that his program would pay for it and that he would find the most distinguished analyst in the Washington, D.C. area. When I told this to Josephine she said, "If they offered to remove your appendix for nothing, would you let them do it?" I turned down the generous offer then but took him up on it a few years later, perhaps because my appendix was finally acting up. Dr. Edith Weigert, probably the senior psychoanalyst in the Washington area, agreed to be my analyst and I spent more than a year in a classical analysis four mornings a week. I found it very pleasant, lying relaxed and talking about myself; I remember dipping into the unconscious very sparingly, but enough to make me aware of its existence.

## The Laboratory of Clinical Science

By 1956, several investigators had joined the Intramural Research Program of the NIMH whose interests were in the interface between the basic neurobiological sciences and clinical psychiatric problems, and a new grouping designated the Laboratory of Clinical Science was established with Ed Evarts as its reluctant chief. By that time, the Basic Research Program was fully staffed. I was eager to involve myself more in research and less in administration, and the implications of the new neurobiological knowledge to psychiatry attracted me. I asked to be allowed to step down from the scientific directorship to join the new laboratory as its nominal chief.

The initial group consisted of Edward Evarts, Julius Axelrod, Louis Sokoloff, Marian Kies, Roger McDonald, who was succeeded by Irwin Kopin, Philippe Cardon, and Seymour Perlin, who was succeeded by

William Pollin. Although quite diverse in their scientific interests, they shared a commonality of motivation and a mutuality of spirit, which made the 11 years I spent in that laboratory one of the most exciting and rewarding periods of my life.

What were these new and promising implications that attracted many of us? It was not the numerous enthusiastic claims that were being made regarding abnormal proteins, metabolites, or toxic factors in the blood or urine of schizophrenic patients, which lacked plausibility and did not survive replication. Rather, it was a number of less spectacular but more credible observations with more remote relevance—observations that suggested that the synapses of the brain, like those in the periphery, were chemically mediated switches rather than electrical junctions. Acetylcholine by that time had achieved the status of a putative neurotransmitter in the brain, but there were other substances like serotonin, noradrenalin, and dopamine, that could conceivably serve in such a role, and which had only recently been identified in the brain. Lysergic acid diethylamide, a drug which had attracted wide attention because of its hallucinogenic properties, had also been found to block some of the pharmacological actions of serotonin. Three other psychotomimetic drugs, dimethyltryptamine, mescaline, and amphetamine were substituted forms of serotonin or dopamine.

Only a few years before, chlorpromazine had been found to be remarkably effective in the alleviation of psychotic behavior and reserpine was being used as a major tranquilizer. Although it was to take 10 years for the action of chlorpromazine on dopamine synapses to be discovered and substantiated, knowledge of the remarkable ability of reserpine to deplete the brain of serotonin was literally around the corner—in Bernard Brodie's laboratory at the Heart Institute. If the synapses involved in the mental states and behaviors produced or ameliorated by such drugs were chemically mediated, those observations would offer plausible sites at which these drugs could act.

Moreover, if central synapses in general were chemical switches, then a biochemistry of behavior was conceivable, and at the synapse, not only drugs, but genetic factors, dietary constituents, hormones, metabolic, immune, and infectious processes, could all be seen to act, altering the patterns of transsynaptic interaction and affecting behavior and mental processes. For the first time, plausible and heuristic approaches could now be opened and explored that might some day explain the biological disturbances of mental illness and the symptoms that depend on them.

The most productive way of exploring these new approaches was not by way of a crash program. The gap between the knowledge we had and the clinical problems was still too wide to be spanned all at once by any concerted effort. What was needed was to narrow the gap by an increase in knowledge on both sides, which is best done by relying on the creativity and judgment of individual scientists who know better than anyone else

what their next step should be. The members of the laboratory pursued their own research goals, some studying the clinical problems in greater detail and in the light of new knowledge, most expanding the base of fundamental knowledge in areas that they perceived to be relevant. Where appropriate, collaborative efforts developed within the laboratory, and quite as often, outside of it. I believe that subsequent events have justified this approach.

Among the claims that were being made at that time was one postulating the formation of a toxic, hallucinogenic metabolite of circulating epinephrine in schizophrenia, which was sufficiently provocative that some of us decided to examine it further. The difficulty was that in 1956 we knew little enough about the normal metabolism of epinephrine, let alone its metabolism in disease. One strategy would be to administer labeled epinephrine in pharmacologically insignificant amounts and compare the urinary chromatographic profiles of radioactivity. The carbon-14 labeled material that was available would not provide sufficient specific activity. It was possible that a tritium-labeled epinephrine could be prepared with the requisite stability and activity, and I made arrangements to have tritium-labeled epinephrine of high specific activity synthesized. By the time the labeled compound arrived, however, that strategy was no longer necessary.

In the year that had elapsed, Axelrod, taking off from a brief report in the literature, had demonstrated the enzymatic O-methylation of catecholamines *in vitro*, characterized the enzyme responsible, predicted the major catecholamine metabolites, and then went on to extract and identify them in the urine of animals. When the radioactive epinephrine became available, it was a simple matter to examine its metabolism in normal subjects (LaBrosse et al., 1961) and in schizophrenics. No evidence was found for an abnormal metabolism of circulating epinephrine in that disorder. There is not the space nor the necessity of indicating Axelrod's contributions to our present knowledge of catecholamine metabolism and inactivation at the synapse. They have not solved a major psychiatric problem as yet, but when the final chapter to our understanding of mental illness is written, his work will occupy a prominent place in it.

Evidence from many quarters produced a general agreement that the biogenic amines were important as neurotransmitters in the brain. Electron microscopy and fluorescence histology were the most direct and compelling, but these were reinforced by microinjection and electrophysiological studies, and by the demonstration *in vitro* of specific receptors for several of the transmitters.

The list of neurotransmitters and synaptic modulators has gotten longer, extending from the biogenic amines to include amino acids and polypeptides. The involvement of specific members of the list in the pharmacological action of most of the psychoactive drugs has been reasonably

well established. It is also clear that neurotransmitters and modulators play important roles in the mediation of certain mental states and types of behavior, although their precise action and interactions remain to be elucidated. It is not possible to state, at present, how they are involved in mediating the symptoms of mental illness or whether they play an etiological role.

In 1961, after struggling with the decision for several months, I persuaded myself that it was not inappropriate for a biologist to serve as chairman of a department of psychiatry and accepted the Henry Phipps Professorship of Psychiatry at Johns Hopkins. Believing as I did that the biological sciences were moving into psychiatry to enrich it and feeling that the search committee at Hopkins had taken a courageous step toward such a rapprochement, I could hardly decline. Despite a plea from a prominent psychoanalyst not to drive another nail into the coffin of psychiatry, but with the encouragement of Aubrey Lewis, whose breadth of understanding and far-sightedness I admired greatly, I assumed the post that Adolf Meyer had made famous. It was not long, however, before I realized that being chairman of a department of psychiatry and psychiatrist-in-chief of an important university hospital entailed more administrative responsibilities far beyond the field of research with which I was comfortable. I resigned after a year with considerable regret.

## The Study of Schizophrenic Adoptees and Their Two Families

In 1959, I reviewed the large number of claims being made of chemical or biological disturbances responsible for the syndrome of schizophrenia (Kety, 1959). Few of these reports survived replication and most could be rejected on the basis of simple scientific design. It was only in the area of genetics that the evidence available seemed a bit more convincing. Of course, the evidence had been available for some time but most psychiatrists had dismissed it because at that time it was not popular to think favorably about genetic factors. Most psychiatrists believed, and few were prepared to contradict the dictum, that schizophrenia was not necessarily a mental disorder, but a way of thinking that one learned from one's parents, which could be treated by education and by psychological and social manipulation. The actual evidence was that schizophrenia ran in families and had a higher concordance in monozygotic (MZ) twins than in dizygotic (DZ) twins. That certainly was compatible with the operation of genetic factors, but fell short of proving it because in each proposition there were alternative explanations, usually invoking environmental influences. So for the clustering of schizophrenia in families: "a lot of things run in families and that doesn't mean they're all genetic." Wealth runs in families. Pellagra and kuru ran in families and were thought to be genetic and genetic models were developed for the transmission of these

disorders. It was eventually discovered that these were dietary diseases and that they ran in families because families shared the same diet. Either a diet poor in vitamin B3 for pellagra, or dietary in the case of kuru because the wife and the children ate the brains of their departed husbands and fathers who were suffering from the slow, viral disease.

In the case of twins, the two most extensive studies by Franz Kallmann in America and Elliot Slater in London were very compelling. Kallmann reported an 85 percent concordance of schizophrenia in monozygotic twins, Slater a 75 percent concordance—which even when conservatively corrected was still about 50 percent. These findings were rejected, however, aside from matters of age correction, for failure to minimize ascertainment and selection bias.

Furthermore, twin studies operate on the assumption that the environmental similarities are the same for monozygotic and dizygotic twins—which isn't true. Monozygotic twins share much more of their environment than do dizygotic twins. They look alike, their parents treat them alike, they parade them in a double perambulator, they dress them alike, they have the same bedroom, and they often sleep in the same bed. They are usually in the same class and they have the same friends. Dizygotic twins have a much greater variance in their environment. It was difficult to tell how much of the high concordance for schizophrenia in MZ twins was the result of the genes or the environment they shared.

Obviously, concordance rates in MZ and DZ twins separated at birth and reared in different environments could produce less ambiguous evidence but there were only single or few case reports and no controlled, systematic studies.

I tried to think of a way to separate genetic from environmental factors in family studies and suddenly realized that adoption did just that: an adoptee shares his genetic endowment with his biological family but his environment with another family. If schizophrenia runs in families because of shared genes, it should be found in the biological family of a schizophrenic adoptee but found in the adoptive family if caused by rearing or other components of the family environment. It seemed reasonable that with appropriate controls to remove ascertainment and selective bias, and with sufficient numbers, adoption could indeed untangle genetic from environmental influences in the family. I suggested this in an article in *Science* (Kety, 1959). "A means of better controlling the environmental variables would be to make a careful study of schizophrenic adopted children with comparison of the incidence in blood relatives and in foster relatives. Perhaps only a survey on a national scale would provide the required numbers of cases."

When I occupied the Henry Phipps chair at Hopkins I was still living in Bethesda and commuting daily between Bethesda and Baltimore. In the course of the hour's drive, I had plenty of time to think about research and

psychiatry, and this question had a high priority. I planned a major study involving a large population, preferably, a national population. Such a study could best be done at the NIMH and without the administrative distractions of a large department. This recurrent and insistent refrain had much to do with my decision to return. When I returned in 1962, I looked forward to undertaking the study I had described earlier by looking in the population of adopted individuals for those who had become schizophrenic, finding their biological and adoptive relatives, then asking the question, "If schizophrenia is familial, in which family of an adopted schizophrenic does the disorder occur, in the biological or the adoptive family, or in both families, or in neither?"

Back at the NIMH I talked to my colleague, David Rosenthal, who had succeeded David Shakow as chief of the psychology laboratory. I found that he was interested in an adoption strategy that would examine the separate effects of family rearing and genetics on adoptees. We recognized that we were dealing with two sides of the same coin. David could use the total sample of adoptees I was planning to acquire, looking for biological parents who became schizophrenic, while I was seeking schizophrenia in the adoptees.

Then we learned that Paul Wender who was a research associate working at St. Elizabeth's Hospital was pulling together a sample of adoptive parents of schizophrenics because he was interested in their characteristics. Are these characteristics different from those of the biological parents? If Ted Lidz is right, the adoptive parents of schizophrenics ought to be just as sick as their biological parents or at least just as schizophrenogenic. We invited Paul to join us in a collaborative effort employing three different adoption strategies. He was beginning to seek adoptive parents of schizophrenics through local adoption agencies, but we realized that this would not be suitable for the studies we were planning. There were about 20 different adoption agencies, each with its own rules and attitudes about research, invasion of privacy, and record keeping. Even if we could get an adequate sample of adoptees, how were we ever going to identify and trace their biological and adoptive relatives in the United States where people are moving around a great deal? Then how would we learn which of the adoptees or their relatives had became mentally ill 25 years later?

Then we learned from Sarnoff Mednick of the remarkable population and psychiatric records in Denmark. They seemed to be just what we needed for the studies we had in mind. I flew over to Copenhagen in 1962 and met with Fini Schulsinger, head of psychiatry at the Kommunhospitalet, who showed me some of the records, introduced me to some of the people, and persuaded the authorities to give us access to their records with our assurances of complete confidentiality. With Schulsinger as a collaborator, we specified the records and the information we would need.

There was no adoption register so it was necessary to develop one. This was possible from the court records required in every legal adoption

in the Department of Justice, which also gave us the names of the biological and adoptive parents. Other registers identified siblings and half-siblings. To ascertain the feasibility of the enterprise, we did a small pilot study and were encouraged to go ahead. With funds from the NIMH Intramural Research Program and a staff recruited by Schulsinger, we undertook my study of the biological and adoptive families of adoptees in the Copenhagen sample who had become schizophrenic, and Rosenthal's study of the adopted away offspring of a schizophrenic parent. We found a total of nearly 5,500 legal adoptions by adoptive parents not biologically related to the adoptee. The results were presented in 1967 at a conference on the transmission of schizophrenia and published in 1968 (Kety et al., 1968; Rosenthal et al., 1968). At the same meeting, Wender presented his study of the adoptive parents of schizophrenic adoptees conducted at the NIH Clinical Center (Wender et al., 1968), the first well controlled test of the "schizophrenogenic parent hypothesis" of which I am aware.

The first findings in the study of the biological and adoptive relatives of adoptees who had become schizophrenic were based entirely on hospital records. They were later augmented by comprehensive psychiatric interviews with the relatives (Kety, Rosenthal, Wender, et al., 1975). A new study of adoptees and relatives in the rest of Denmark (*The Provincial Study*) provided a replication of the Copenhagen study which doubled the number of subjects, confirmed the previous results, and increased their significance (Kety, Wender, et al., 1994). In all of Denmark, 47 adoptees were found who had developed chronic schizophrenia; their biological relatives—parents, siblings, half-siblings—showed a prevalence for that disorder of 5 percent compared with 0.4 percent in the biological relatives of 47 normal adoptees. No schizophrenia was found in the adoptive relatives of the schizophrenic or control adoptees.

These studies were highly consistent in finding schizophrenic illness significantly concentrated in the biological siblings, parents, and offspring of schizophrenic patients even when separated by adoption. Adoptive parents who had reared a schizophrenic adoptee in Wender's study (Wender et al., 1968) had none of the characteristics attributed to schizophrenogenic parents.

These studies had an impact on the field because of the unique and rigorous design (case-matched controls, blind diagnoses, lack of ascertainment, selective, and subjective bias), and because they strengthened the argument for genetic factors in the earlier family and twin studies by ruling out alternative possibilities and failed to support schizophrenogenic rearing in the etiology of schizophrenia.

## NIMH Turns Away from the Brain and Mental Illness

In circumstances prevailing in other branches of medicine, the demonstration of the chemical nature of synaptic transmission, the develop-

ment of drugs capable of alleviating the symptoms of mental illness quite specifically, and the elucidation of their synaptic actions— as well as the new evidence for genetic factors in the etiology of the major psychoses—would have ushered in an era of widespread public and professional support for the exploitation of the new research opportunities that were then presented. But it was not to be as simple as that. The NIMH became dominated by quite a different philosophy in which the kind of research that I had espoused lost its high priority, and basic research, biomedical research, and even research on schizophrenia and mental illness was disparaged.

Support of research requires a recognition of ignorance and the community psychiatry movement in the United States brooked no doubts regarding its convictions on the social etiology of mental illness and the types of social engineering required in order to treat and prevent it. The NIMH broke away from the NIH, much to the frustration of James Shannon, the great director of the NIH. He did insist, and was successful, however, in keeping the Intramural Research Program intact within the NIH and under the judicious and courageous leadership of John Eberhart.

The remainder of the NIMH was reorganized, in the course of which the Division of Extramural Research was fragmented and parochialized. Research in the fundamental neurosciences was unsupported on the premise that these had little relevance to psychiatry. I shall never forget the meeting I attended at which psychiatry as a branch of medicine and rigorous science was gutted and exorcised from the Grants Program. Stanley Yolles, Bob Felix' successor as director of NIMH, had called the senior staff together for a weekend retreat, presumably to help formulate the objectives and structure of the new NIMH. We amused ourselves individually while the director was closeted with his two or three henchmen until Sunday afternoon when we were called together to see and possibly to discuss the new table of organization and structure of the institute. I was shocked. The branches and study sections responsible for evaluating research proposals and allocating funds, traditionally designated to span a wide spectrum of basic disciplines and clinical areas, were all reduced to a repetitious melange of community cliches: metropolitan problems, adolescent problems, minority problems, and social problems, to mention a few. There were surprisingly few comments from the floor. I confessed to being disappointed, pointing out that there was no place in the table for basic research, for biomedical research, or even for research on schizophrenia. There was no logic and no justification for organizing the national program on mental health and illness on such an arbitrary and narrow pedestal. Yolles commented that it didn't have to be logical if it was what the Congress wanted. There was no evidence that this had been mandated or even emphasized by Congress and no recognition of the responsibility for scientific leadership that resided with institute directors.

I readily accepted an invitation from Harvard to organize a program of psychiatric research at the Massachusetts General Hospital and later at the McLean Hospital. I did not feel that I was fleeing a sinking ship since the Intramural Research Program was in excellent hands with its future assured. I was concerned with the Extramural Program and recognized an opportunity of broadening it from the outside. Fortunately, I was able to recruit or co-opt an excellent consortium of young scientists, and a few senior scientists like Walle Nauta, Alfred Pope, and Philip Holzman who were willing to participate in a research program like that of the Laboratory of Clinical Science at NIMH. We put together a compelling and broad program justifying a substantial budget and submitted it to the Research Grants Division of the NIMH without seeking the advice of the extramural staff who expected to be consulted on any substantial application. The proposal received very fair treatment; reviewed by an outstanding *ad hoc* group for a priority of 1.0, we were awarded the grant. I had hoped that this might initiate the establishment of a branch devoted to multidisciplinary research in mental illness. It did stimulate the submission of a similarly successful proposal from Yale but no branch.

Some years later, I asked Axelrod to join me in a visit to Bertram Brown, who had succeeded Yolles but retained a similar agenda as director of the NIMH. I knew that Brown was taking gratuitous pride in Axelrod's Nobel Prize and we had a simple request to make. Would he consider establishing a Neuroscience Branch or Study Section in his Extramural Program? I was not expecting to be turned down, but we were, flatly. The reason generated a *déjà vu*—he had no constituency requesting it. No matter that the best scientists are more interested in their research than in polishing their political clout, or that the director's responsibility was to plan and advocate a competent research program rather than to cater to self-serving pressure. Thus, for more than a decade, the NIMH turned its back on neuroscience, leaving it mainly to the National Institute of Neurological Disorders and several of the other institutes to sponsor, support, and take pride in the burgeoning development of an exciting field which continues to hold great promise for an understanding of mental illness.

I may have been more successful turning the People's Republic of China around (Kety, 1976). I was asked to join the first official biomedical delegation from the National Academy of Sciences and the Institute of Medicine to the PRC in 1973, to represent neuroscience, neurology, and psychiatry. I met the professors of neurology and neurophysiology (many will recognize the name of Professor Chang in Shanghai) but no psychiatrists. I was told there were no departments of psychiatry at the medical schools and in hospitals we visited because there was no mental illness. In Beijing I asked to meet Professor Wu Chen Yi whom I knew from the

literature but to no avail. At the state banquet in our honor I made a toast "to the psychiatrists of China, wherever they may be."

Toward the end of our stay in Beijing we met with Dr. She Hua, minister of health, who told us about the progress his country was making in eradicating various epidemic diseases. When we were invited to ask questions, I ventured:

> We have all been impressed with the accomplishments you have enumerated, but you have omitted the topic of mental illness which we in the West regard as a major public health problem. We have been told that there is no mental illness in China and if that is the case that is the greatest accomplishment of all. We would like to know how you have done this; in fact, there is a group of psychiatrists eager to visit who will want to talk to me when I return. Shall I encourage them or tell them that this is not the right time?

She Hua smiled warmly and responded: "We have our share of mental illness, but we treat it differently now than previously. We don't put such patients in dungeons but in mental hospitals where they talk to doctors and nurses and among themselves to learn more about their problems. We also use drugs, Western drugs. Your colleagues from America are welcome to come here at any time to exchange knowledge with our psychiatrists." There were numerous officials present at this meeting who must have taken She Hua's statement as a change of policy. It was certainly followed by a remarkable change in whom I could meet.

The next day we visited the Great Wall, each in the company of a counterpart. I rode with the editor of the *China Medical Journal* and held forth on what has recently become our concept of mental illness—disorders representing an interaction of genetic and environmental influences. I contrasted that with the official attitudes I have observed in most communist countries where genetic differences are denied since all are created equal and, since the environment has been cleansed of all untoward influences, there remains little opportunity for mental illness to develop. At a reception back in Beijing I was happy to meet Professor Wu Chen Yi who invited me to give a lecture in his department at Beijing University.

When our plane landed at the Shanghai airport, I was greeted by Professor Yen, who invited me to visit his large mental hospital where I saw schizophrenic patients treated with acupuncture and with chlorpromazine.

It was most gratifying to visit China with my wife a few years ago at the invitation of the China Medical Society to receive an Honorary Professorship at Shantu University where Professor Wu Chen Yi directed a beautiful psychiatric Institute after his retirement at Beijing and

Professor Yen was the psychiatrist-in-chief at a large and modern Mental Health Center in Shanghai.

Our own NIMH to which I have returned after retiring at Harvard, had also experienced a major renaissance. Bertram Brown was succeeded by Herbert Pardes who recognized the importance of rigorous basic and clinical research, the excitement of the neurosciences, and began a major transformation of the Extramural Program which each of his successors—Shervert Frazier, Lewis Judd, and Fred Goodwin—has continued. The institute has rejoined its Intramural Program and shares the scientific traditions of the NIH to which it has returned.

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