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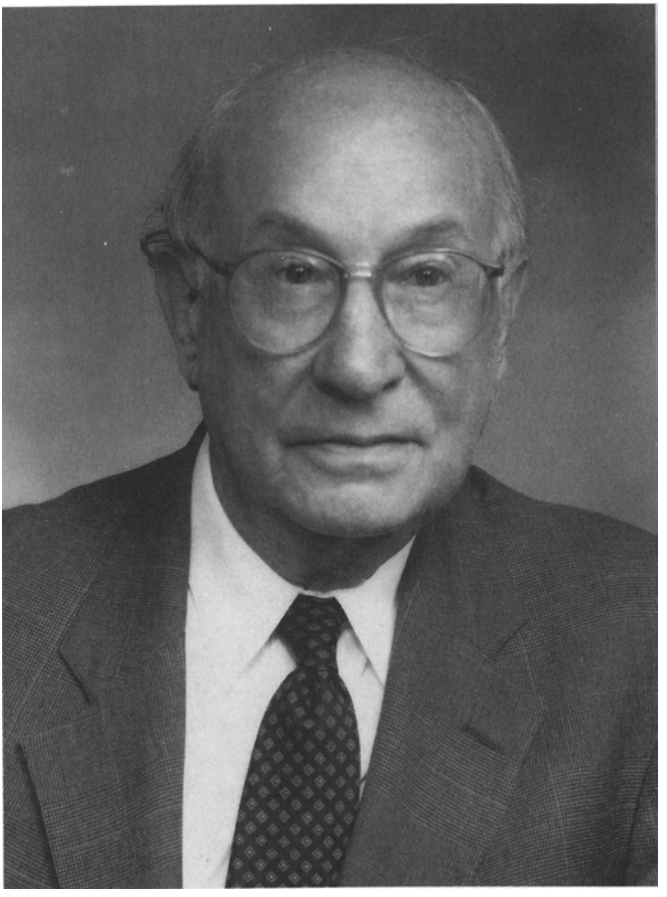

Louis Sokoloff

BORN:

Philadelphia, Pennsylvania
October 14, 1921

EDUCATION:

University of Pennsylvania, B.A., 1943
University of Pennsylvania, M.D., 1946
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American Society for Neurochemistry (President, 1977–1979)
National Academy of Sciences USA (1980)
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American Academy of Arts and Sciences (1982)
Association for Research in Nervous and Mental Disease (President, 1983)
Karl Lashley Award (American Philosophical Society, 1987)

Louis Sokoloff began his scientific career as a student of Seymour Kety, and went on to develop the 2-deoxyglucose technique for measuring quantitatively regional metabolism in the brain. This led directly to the invention of revolutionary noninvasive methods for functional imaging of the human brain.

Louis Sokoloff

It is with some uneasiness that I undertake the preparation of an autobiography. For 45 years, I have been totally immersed in scientific research and have written many scientific articles in the traditional style, which required that a report be impersonal with only its scientific content of consequence. Indeed, I still shrink from the use of personal pronouns and rely heavily on the passive voice. This is the tradition, probably more idealistic than realistic, in which only truth, and not people, is of significance. Rigorous attention to accuracy and proper documentation is paramount. In this autobiographical sketch, I am forced to rely on memory, and I learned at a 1995 meeting of the Association for Research on Nervous and Mental Diseases on learning and memory that recalled memory may be more imaginative than real. Nevertheless, my commitment is made, my task is clear, and I shall do my best to relate those events in my life that are of significance to my career as a neuroscientist with as little distortion of the truth and as much freedom from self-serving bias as I can achieve.

Origins and Early Years

Like almost all my American colleagues of a "certain age," which I shall not define, I belonged to the generation that President Franklin D. Roosevelt had labeled in his initial inaugural speech as one that had a "rendezvous with destiny." We were certainly influenced, indeed shaped, by the momentous and historic events that evolved during the most critical periods of our physical and intellectual development. In our childhood and adolescence, we lived through the Great Depression, and then, as we were emerging from that economic crisis and entering young adulthood, we were confronted with the challenges of World War II. I believe that it is a fair statement that nothing in my personal, intellectual, and professional life was not directly or indirectly influenced or derived from the impact of those cataclysmic events.

I was born in Philadelphia, Pennsylvania, the second son of immigrant parents. My father had emmigrated alone as a young man from the Ukraine in 1912. No one else from his family ever came; he left a mother and sister there whom I never met, with whom I never had any contact, and whose fate is unknown to me. He came from a city, perhaps a village, that was then known as Elisavetgrad but, according to my current

Russian postdoctoral fellow, is now the city of Kirovograd. My mother, the oldest of six children, had quite independently also arrived in the United States in 1912. She accompanied her father from a town now in Poland that was then just on the Russian side of the border between Russia and Germany; I do not recall its name. Her mother, four sisters, and a baby brother were brought over shortly afterward. All had emmigrated to the United States to escape czarist persecution and the ravages of pogroms, which they were reluctant to describe but to which they occasionally alluded. My parents met in Philadelphia not long after their arrival and married; my brother was born in 1915, and I in 1921. It was about 1924 that my father attained American citizenship; my mother became a citizen some time later.

I was born at home in a row house in South Philadelphia, which we owned and in which we lived until we lost it during the Great Depression when I was about 11 or 12. The physician who delivered me remained our family doctor until I was in medical school. South Philadelphia is notorious as a tough neighborhood. Its residents were largely poor and working class; many were immigrants or first generation Americans, and they represented a variety of national origins: German, Hungarian, Irish, Italian, Polish, and Russian. The residents of our street were mainly, but not exclusively Jews, both native born and of Eastern European origin. I can recall no evidence of tension among the ethnic groups living in the immediate neighborhood, but we did have street gangs that engaged in fights that were more territorial than racial, ethnic, or religious. I belonged to the Third Street Gang, and we had prearranged rumbles with the American Street (the next street) gang. Our weapons were halves of broken paper clips fired from rubber bands. Such street battles were held until one of the participants lost an eye in a battle.

The most prominent influence in my early years was the emphasis my parents placed on education. Neither had had much formal education. My father's formal education ended when he was about 12 and was forced to work to support his mother and sister after his father's death. It was then that he learned the tailoring trade that helped us to survive during the depression years. My mother, as the oldest daughter, had learned to keep house, which she did very well; she kept an immaculate home and was an outstanding cook, which, except for her two sons, was the source of her greatest pride. Possibly because of their lack of education, they valued their childrens' education above all else. They could not help us directly but gently coerced my brother and me to do our homework and to do well in school, and we did. I vividly remember my grandfather asking me what I wanted to be when I grew up. At that age, of about 5 to 10 years, it was probably something that we considered heroic, such as a cowboy, policeman, or sports hero. His response never left me. He advised me to choose a profession, any one, in which all my significant possessions would reside in my mind because, being

Jewish, sooner or later I would be persecuted and would lose all my material possessions; what was contained in my mind, however, could never be taken from me and would accompany me everywhere to be used again.

Emphasis on education and Americanization permeated the home atmosphere. Though both my parents spoke Russian, they never did so to my brother and me, something that I strongly regret. I do recall a Russian phrase, which as a child I had heard my father exclaim when he had hit his finger with a hammer while hanging a picture. I have since learned its meaning; it is not repeatable here. That probably explains why I never heard my father use any vulgar or improper expletives in English; he resorted to Russian, which the children did not understand. We did speak some Yiddish at home, which I used mainly to converse with my grandparents, and I also learned to read Yiddish newspapers. To my regret, my knowledge of Yiddish was almost completely erased when I later studied German in college. I became fluent in German and comfortably conversed with my grandfather, but when I later made a serious effort to learn French, it more or less displaced the German. Apparently my brain is capable of retaining only one foreign language at a time.

My earliest memory of gifts given me by my parents is of two used volumes of the *Baldwin Reader* and a worn faded copy of a book titled *First Steps in the History of Our Country*, which my father had bought at Leary's Bookstore, then the oldest bookstore in the United States. The book cover was maroon in color, and on its front was an oval cameo of the head of George Washington in profile. Each chapter of the book was devoted to a historic figure who had contributed in some way to American history; among them were Washington, Jefferson, Lincoln, Jackson, Grant, and Boone. The story that had the longest and strongest affect on me was the one on James Wolfe, the general who led the English army in the capture of Quebec and ended the French and Indian War in 1759. The chapter describes how on the evening before the decisive battle, Wolfe sat on the deck of a boat that went back and forth on the St. Lawrence River ferrying the English troops to Wolfe's Cove, where they could scale the heights to the Plain of Abraham above. Sitting on the deck surrounded by his staff, Wolfe repeated over and over again the following verse:

> *The boast of heraldry, the pomp of pow'r,*
> *And all that beauty, all that wealth e'er gave,*
> *Await alike the inevitable hour.*
> *The paths of glory lead but to the grave.*

Finally, after the last boatload of troops had disembarked and the first lights of dawn were breaking in the east, Wolfe arose and stated, "Gentlemen, I would rather have written that verse than take Quebec today." What impressed me most was the final sentence of the chapter, "No one responded because none dared to say that the soldier was greater

than the poet." Obviously, I was taken by the story and the verse, for I still remember it after so many years. Some time later I learned that the verse was from Gray's "Elegy Written in a Country Churchyard" and was struck by another of its verses,

> *Full many a gem of purest ray serene*
> *The dark unfathomed caves of ocean bear.*
> *Full many a flower is born to blush unseen*
> *And waste its sweetness on the desert air.*

The fatalism in the poem's message resonated in me. Perhaps because of my genetic make-up, cultural heritage, or early experiences in a difficult time, I developed a pessimism and stoicism that has always led me to hope and work for the best but to expect the worst, and, in the words of Rudyard Kipling, to "meet with triumph and disaster and treat those two impostors just the same." This may come as a surprise to those who have served in my laboratory because I always tried to exhibit to them a spirit of optimism in the conduct of research. In directing a research project, I always revealed to my co-workers the potential and anticipated obstacles only one at a time because I have seen good ideas too often throttled at conception because of intimidation by anticipated problems to be solved.

As soon as I learned how, I read avidly and broadly, an activity facilitated by proximity to a branch of the Philadelphia Public Library about a block away from our home. William Penn's original design of the city specified that streets be arranged in checkerboard fashion with each block 0.1 mile in length.

I studied hard and did well at school, but my greatest passion was baseball. I followed the fortunes, or more often the misfortunes, of the Philadelphia Athletics, now in Oakland, and the Philadelphia Phillies. My heros were Al Simmons, Mickey Cochrane, Jimmy Foxx, and Lefty Grove of the A's and Chuck Klein of the Phillies. Although I was small for my age, I tried to participate in the sport and was a mediocre second baseman or shortstop on a boys' neighborhood baseball team, the Centennials. We could not afford uniforms and settled instead for blue baseball caps with a white C on them. The name was probably suggested by the sesquicentennial celebration of the Declaration of Independence in Philadelphia in 1926.

The Depression and Secondary School Years

It would have been nearly impossible to grow up in an industrialized area like Philadelphia during the Great Depression without developing serious misgivings about an economic system that created and allowed the severe injustices and hardships inflicted on a major portion of the population. From the age of eight and continuing through my teens, I was wit-

ness to large numbers of proud and able-bodied men reduced to begging; masses of people going hungry; professionally trained people selling pencils, shoelaces, apples, anything to earn enough to feed themselves and their families. I will never forget the beggar who rang our doorbell one evening, and when presented with a penny, he returned it and asked for food instead because he was hungry; he then ravenously consumed the food that my mother offered him in our kitchen. Experiences such as these stimulated in me an intense interest in political affairs, economic issues and systems, and history, particularly of modern Europe. I zealously read newspapers, news magazines, any periodicals that I could find in the public library, and followed with trepidation the rise of Nazism in Germany, the invasion of Abyssinia by the fascist forces of Italy, and the twilight of the League of Nations. Many of my school and neighborhood friends and acquaintances became inquisitive about and experimented with economic systems alternative to capitalism. I myself developed an interest in the platforms of the Socialist Party led by Norman Thomas and often argued vociferously but unsuccessfully with my father, a loyal Democrat, that he should vote Socialist. Some of my classmates actually joined the Young Communist League (YCL). Fortuitously in the light of later events, that is, the period of MacCarthyism in the United States when I came to work for the Federal Government at the NIH, I managed to avoid joining any politically active organization. My participation in political affairs was more intellectual than activist. That was probably because I was fervently anti-communist, and on the basis of my own experiences and those of my communist colleagues, I was wary of the danger that organizations with ostensibly respectable and desirable goals, such as the American Youth for Democracy (AYD), the Association of Interns and Medical Students (AIMS), and the Association of Scientific Workers (ASW), were, in fact, a front for the promulgation of communist ideology and goals, which I believed to be mainly foreign policy objectives of the Soviet Union.

Our family did not escape the ravages of the depression. My father was employed as a finisher of fur coats—one who sewed linings in the coats—in the firm Mawson, DeMany, and Forbes. Luxury items like fur coats were hardly in fashion during the depression. The company was forced out of business, and my father was then unemployed at a time when there was still no social security or unemployment insurance in the United States. As a result, we lost the house because of inability to pay the real estate taxes, and when I was 10 or 11 and in the fifth or sixth grade, we moved to a much smaller rented house. It was only about three or four blocks from the previous home, and I did not have to change schools. The move was, nevertheless, traumatic. It meant leaving old and familiar friends with whom I had grown up, socialized, and played baseball and other games. It meant becoming a stranger in a new milieu where I would have to make new

acquaintances and friends, a difficult prospect for me at the time because I was shy and introverted. It was, of course, a trivial experience compared to that of my parents who had to leave members of their family and emigrate to a new country with a new language, but I did not think of that then. It turned out, however, to be a fortunate move for me, for it did eventually have favorable consequences for my future intellectual development.

The new home was located on a small side street where it was easy for the residents to know and associate with one another. The row houses had open front porches, which the residents used to escape the oppressive heat and humidity of summer evenings. They also sat in rocking chairs on the sidewalk to catch the breezes. Air-conditioning was found only in movie houses and department stores. Most of the families, therefore, knew each other quite well, were often friends, and frequently helped one another through financial and other crises that were so frequent during the depression.

Five houses down from us on the same side of the street there lived a man, Israel Abrams, who was in his twenties and taught mathematics first in a junior high school and then in a high school in the Philadelphia public school system. He was one of those who often sat on his front porch, and perhaps because he had learned that I was a serious student, he took an interest in me, my studies, and my ambitions. By the time I met him, my interest in science, particularly biology, had already been more or less fixed, and he guided and advised me in my reading and thinking about science. Abrams was also an avid tennis player, and when I was about 12, he gave me a tennis racquet that he was replacing. That introduced me to a sport that I once passionately pursued and still enjoy. Tennis lessons were unaffordable, but I tried to model my game after those of touring professionals who annually played at the Philadelphia Convention Hall. Among them were Ellsworth Vines, whose service style I imitated, Fred Perry, whose forehand I tried to copy, and Don Budge, whose incredible backhand I tried unsuccessfully to emulate. Unlike my experience in baseball, I did develop some skills in tennis, enough at least to play in the number one singles position on my high school tennis team for three years. However, our team perpetually occupied last place in both the Public High School and Interscholastic Leagues, and I won only three matches in those three years. One of my losses was to Victor Seixas, who was then the National Boys' Champion and later won championships at Wimbledon and Forest Hills and who, with Tony Trabert, brought the Davis Cup back from Australia to the United States.

My interest in biology began at an early age when my brother set up a balanced aquarium of tropical fish, plants, snails, and so on. I was intrigued by that community of living things and spent hours observing it as well as reading about aquarium animals and plants. I studied the anatomy, classifications, habitats, and diseases of fish and aquatic plants, and I still have a card file on the various species used in aquaria. There

was a time when I thought of becoming an ichthyologist but was dissuaded from that by Abrams. My reading then expanded to biology and science as a whole. Like many of my generation, I was greatly influenced by Paul De Kruif's *Microbe Hunters*, as well as by Donald C. Peattie's *Green Laurels* and Eric Nordenskiöld's *History of Biology*. Another book that I spent hours reading was *Chemistry in Medicine*; it was distributed free by the Chemical Rubber Company by request on a penny post card. Each chapter in the book was devoted to a specific medical or biological problem and described the research that had contributed to its solution, such as discovery of vitamins and the cause and cure of pellagra, the development of germ theory, and the work of Pasteur, Koch, and Metchnikoff. A life spent in biological research then seemed attractive, and that goal was encouraged by Abrams.

The depression was severe during my years in the secondary schools, but it nevertheless had a salutary effect on the quality of my education. Jobs were scarce, but teaching positions in the Philadelphia public schools were among the best and eagerly sought. Consequently, we had excellent and dedicated teachers, a number of whom had doctoral degrees. Some had left university faculty positions because of the better salaries and security in the public school system. From Furness Junior High School I particularly remember Mrs. Micocci, whose enthusiasm and good humor made even the writing of English compositions relatively painless; Mr. Paravacini and Mr. Kappel, who made the study of mathematics fun; Mr. Kaplan's stimulating classes in history made even more vivid and relevant by the momentous events in Europe precipitated by the antics of the Nazis in Germany and the Fascists in Italy; and the patience, dedication, and innovativeness of Miss Lynn, who taught us General Languages and Latin. I had no skill at all in art, and as hard as he tried, Mr. Koppelman could detect no trace of artistic talent in me. The effectiveness of the teaching was enhanced by the nature of the student body. Most of us were from immigrant families imbued with the virtues and importance of education. There were almost no disciplinary problems; the few that occurred were dealt with quickly, firmly, and decisively.

I later attended the South Philadelphia High School for Boys. There had once been only one high school, but the boys and girls were separated into two schools because of the high incidence of illegitimate pregnancies. It was a tough school in a tough neighborhood and fully consistent with the national reputation of South Philadelphia. The school was located in an area known as "Little Italy" because of its large population of Italian immigrant families, mostly from Sicily and Naples. The student body, however, was multiethnic and multiracial and included Poles, Russians, Irish, Jews, Germans, an occasional black, and sometimes even one of Anglo-Saxon origin. Marian Anderson had gone to the girl's high school, and Mario Lanza, then known as Alfredo Cocozza, was there two years ahead of me. Despite

its reputation for toughness, it was an excellent school, second in academic standing only to Central High School, which was located in central city and was limited to specially qualified students. There were many students in our school, including me, who could have qualified but never applied because they could not afford the trolley fares needed for transportation. School buses were then available only for handicapped children, many of whom went to special schools. Unlike my junior high school, this school required faculty who were not only good teachers but also strict disciplinarians, and they were firm and strict indeed. The principal was Frank Nieweg, which in German means "never away," and he lived up to his name. He did not hesitate to suspend or even expel students who did not adhere to accepted codes of behavior. Even smoking on school grounds was cause for suspension. Requirements were high, grading was severe, and teachers did not hesitate to fail students who did not meet the standards. George Kimmelman, who taught senior class English, routinely failed about one-third of the class in the first grading period, about a quarter in the second, and as much as 10 percent in the final grades for the term. Failure in a major subject meant repeating not only the course but the entire grade as well. Mr. Feick taught us physics, and he was extremely rigorous and demanding. On one of his examinations, I received a score of 98 with no obvious reason for the deduction of two points. Although I was happy with the grade, I was curious and inquired about the loss of the two points; it was because I had left out two commas in my examination paper. Mr. Wolfe taught us chemistry and constantly admonished us never to believe anything unless we had positive evidence to support it, certainly good advice for a budding scientist. Other more humane teachers were Dr. Eilberg, a geometry teacher, who liked to challenge us by betting us pennies that we would be unable to solve problems in geometry that he selected; I collected a lot of pennies. I particularly enjoyed Mr. Egnal, a history teacher, and, Mr. Gregory, who taught biology, probably because both served in sequential years as the coach of the tennis team of which I was a member. In my senior year, when I was concentrating on my studies to achieve the grades needed to win a Board of Education scholarship to one of the universities, I considered resigning from the tennis team; it was Mr. Gregory who dissuaded me, arguing that he himself had once faced the same dilemma and found that the athletic activities and the diversion they provided actually improved his academic performance.

The depression weighed heavily but not entirely unfavorably on my intellectual development. My father was frequently unemployed or on strike. Fortunately, his tailoring skills were sufficiently diverse so that he could find work in the manufacture of men's suits or women's dresses when work in the fur trade was unavailable. Most of our neighbors and school associates were in similar straits. Because we could not afford material things, my friends and I found recreation in sports and intellectual dis-

course. We spent many of our free hours discussing literature, history, philosophy, science, and political and social issues. We learned to construct or assemble from parts obtained cheaply in junk yards various objects that our families could not afford. For example, we built our own radios, beginning with crystal sets and progressing to short wave sets. We wound our own coils with enamel-coated wire on the cardboard cylinders from rolls of toilet tissues. I can vouch that the sound from one's own constructed radio is far more pleasing than that from a purchased radio or hi-fi set.

The College Years

It was clear that the family finances would not support college educations for my brother and me; our only recourse was to obtain scholarships. Inasmuch as athletic scholarships were out of the question, we would have to gain them by scholastic achievement. The Philadelphia Board of Education provided two scholarships for each high school graduating class, one to the University of Pennsylvania (Penn) for the top student in the class and the other to Temple University for the second. There were also Mayor's Scholarships to the University of Pennsylvania, which were granted on the basis of competitive examinations. My brother, who was six years ahead of me, came in third in his class and missed out on either of the Board scholarships, but the following year he won a Mayor's Scholarship. I was more fortunate; I was first in my class and thus was also able to attend the University of Pennsylvania for the following four years.

When I entered college in September 1939, I had already decided on a career in biology. That decision was fully consistent with my previous leanings, but it was undoubtedly also influenced by the fact that my brother had majored in zoology in college. As we lived at home, I had access to his books, and while still in high school, I eagerly studied his biology textbooks. From his Guyer's *Animal Biology*, I learned thoroughly the taxonomy of the animal kingdom and all the phyla and classes and, indeed, much more. I found it all fascinating. At that time, Penn had separate botany and zoology departments and offered majors in either one or the other but not in biology. I was inclined toward zoology. Job opportunities for zoologists, however, were scarce during the depression, and alternatives had to be considered. In high school I had already considered medicine or veterinary medicine as acceptable alternatives. Naively, I thought that medicine was merely applied biology.

Penn then had no specific premedical curriculum. Students interested in medicine matriculated in a liberal arts and sciences curriculum and added to the core curriculum the courses required for admission to medical school. Some of the courses in the first two years were prescribed, that is, English literature and composition, foreign language, mathematics, history or philosophy, and science. In my first two years I chose for my sci-

ences zoology, botany, inorganic and organic chemistry, and qualitative and quantitative analytical chemistry; in subsequent years I added physics, physical chemistry, and various courses in zoology. My foreign language choice was German because before the Nazi period German science was predominant, and it was customary for scientists to spend some time studying in Germany.

Three successive semesters of English composition were required, the first one on narration, the second on description, and the third on exposition. In the first two courses, we generally had to write a composition each week. The course on exposition required us to write feature or special articles that needed more time; for example, I wrote one titled "Unclean! Unclean!" which was a history of leprosy through the ages. The standards were kept high, and the grading was rigorous. Mistakes in grammar were treated seriously. Dangling participles were unacceptable, and a run-on sentence resulted in a failing grade for the composition. This experience is probably responsible for my continued rigid insistence on proper language usage that my fellows and collaborators have known too well. There was one experience in my second semester of English composition that I still vividly recall. One of the students objected to our having to write a composition every week and asked how that would help him earn a better living. The instructor, Mr. Lee, responded, "You don't go to college to enrich your pocket book; you go to college to enrich your mind." I fear that this sentiment is now lost in antiquity.

One memorable course was Modern European History, which lasted from September 1940 to May 1941. The first semester covered the period from the Congress of Vienna to the beginning of World War I; the second continued from then right up to the last day of the course. One-hour lectures were given at 9 a.m. every Monday, Wednesday, and Friday by William Lingelbach, an eminent historian who was also dean of the College of Arts and Sciences. A syllabus had been handed out in advance that listed the topics of each of the lectures, and the topic of the last lecture was "Europe—Subject to change without notice." The ambiguity amused the class, for it was a time during World War II when the Nazi hordes were rampaging throughout Europe, and we were uncertain whether it was Europe or the subject of the lecture that was subject to change without notice. On the morning of the last lecture, the front-page headline of the *Philadelphia Record* heralded the airborne invasion of Crete by the Germans. The lecture that morning was on the battle of Crete, and it was extraordinarily scholarly and erudite; it gave a brief history of Crete and its strategic importance to both the Germans and the British in the war.

Major fields of study were selected in the second year to begin in the third year, but this choice became a family problem. I was committed to zoology, but my brother convinced my parents that opportunities for zoologists during the depression were limited and that I would have difficul-

ty obtaining employment after graduation unless I were admitted to medical school. Admissions to medical schools, however, were then quite limited for certain minorities, such as Jews. The family recommended that I major in chemistry because prospects for employment were better for chemists than for zoologists. I resisted but agreed to a compromise. Zoology would be my major, but I would in addition choose as electives all chemistry courses required of chemistry majors. This was fortunate, for not only did I enjoy chemistry, but the background in chemistry later proved to be useful and, indeed, played a role in directing my interests toward biochemical and metabolic processes.

It was in my third year at Penn that I was exposed to my first research experience. Lewis V. Heilbrunn in the Department of Zoology taught a mixed graduate–undergraduate course in general physiology, which was essentially cellular physiology with little organ or system physiology represented. Prerequisites for the course, in addition to the basic chemical and biology courses, were physics and physical chemistry, both of which I was also taking in my third year. Because my academic record was quite good, Heilbrunn accepted me even though I had not yet completed all the prerequisite courses. It was an enlightening experience and more than anything, influenced me to choose a career in scientific research. The atmosphere was exciting, indeed exhilarating. Heilbrunn was analytical and critical, sought definitive and rigorous explanations of biological phenomena in terms of physical and chemical mechanisms, and was impatient and even brutal with loose logic. He was readily accessible to the students and seemed to revel in their company. For example, Heilbrunn and his wife, the artist Ellen Donovan, frequently held open house on Saturday nights, and his graduate and undergraduate students often congregated at their home at the end of the evening. Often there were other guests, friends, and associates of the Heilbrunns, who would add to the richness of the company. Those were highly intellectual evenings, with discussions about a variety of subjects in the arts, sciences, and humanities. The culture and life of the academic scientist seemed to be full and rich, and I was attracted to the choice of such a career.

Heilbrunn's course extended over two semesters. It included two hours of lecture and four hours of laboratory work per week. Heilbrunn's lectures, like his textbook (Heilbrunn, 1938), strongly espoused his ideas about the role of calcium in biological processes. Earlier work of his colleagues, D. Mazia and J.M. Clark, had stimulated some of those ideas. Heilbrunn had previously recognized the role of calcium in the maintenance of cell membrane integrity and in the regulation of intracellular protoplasmic viscosity. Mazia and Clark (1936) showed that electrical, osmotic, or mechanical stimulation and ultraviolet radiation of *Elodea* cells caused almost instant formation of calcium oxalate crystals in the vacuoles of the cells that were known to contain high levels of oxalic acid.

The only reasonable explanation was that the stimulations were associated with an almost instantaneous rise of intracellular ionic Ca^{++}, probably by release from bound sites. From these and many other observations, Heilbrunn hypothesized that release of free Ca^{++} was an essential component of the processes of excitation, conduction, muscular contraction, blood-clotting, secretion, and so on. These are ideas that today are almost taken for granted, but at that time Heilbrunn's was almost a lone voice in the wilderness. He so forcefully pushed these ideas in his lectures that at the end of the final examination for the first semester of the course, one of the students led the class in a college cheer, "C-a-l-c-i-u-m! Calcium! Calcium! Calcium!"

The laboratory portion of the course consisted of a series of prescribed exercises at the beginning of each semester, followed by an original research project during the remainder of the semester. It was impossible to complete the prescribed experiments, let alone the research projects, in the time allotted to laboratory work in the roster, and students routinely returned during evenings and weekends to complete their work. Heilbrunn and his graduate students and assistants were often there, and much time was spent not only in scientific discussions but also in anecdotes related by Heilbrunn about himself and some of his famous scientific colleagues. He made all of us, even the undergraduate students, enjoy the exhilaration of being involved in the process of scientific inquiry and discovery.

My research project during the first semester was suggested by Heilbrunn. It was to determine if protoplasmic flow in the pseudopod of the *amoeba* obeys Poiseuille's Law. I can quickly summarize the results: it does not. My project in the second semester was suggested by Daniel Harris, an instructor who had obtained his Ph.D. with Heilbrunn. The project was to fractionate cells and localize enzymes to the subcellular components. This was several years before the isolation of mitochondria by Hogeboom et al. (1948). The cell I chose for study was the unfertilized frog egg, probably more for economic than scientific reasons. The cells were homogenized and separated by centrifugation into plasmasol (the term used then for cytosol), lipids, yolk, and pigment fractions. We localized lipases to the lipid fraction, dipeptidases to the plasmasol, and a few other enzymes that I no longer remember. The results do not seem interesting now, but that experience in research had an important influence in shaping my goals for the future.

Its immediate effect was to persuade me to choose as an elective in my final year "Zoology 50, Undergraduate Research in Zoology." That course enabled me to continue research with Heilbrunn. The United States was then in World War II, and Heilbrunn had obtained a grant from the U.S. Army to study effects of heat on biological systems because the British 8th Army had suffered numerous heat-related casualties in the deserts of Egypt and Libya. Most of his group were assigned to various aspects of

this problem. I was given the assignment to determine in the rat sciatic nerve-gastrocnemius preparation, which was more sensitive to heat—nerve or muscle. Electrodes were applied to both the nerve and the muscle, and a lever-pen assembly to register contractions was attached to the muscle. Either the muscle, the nerve, or both were immersed in Ringer's solution at 41°C, and alternately the nerve and the muscle were electrically stimulated until the muscle stopped contracting. When nerve alone was heated, the muscle responded to either nerve or muscle stimulation for prolonged periods. When only the muscle was heated, muscle contractions in response to nerve stimulation ceased in 5 to 10 minutes but continued to be elicited by direct faradic stimulation of the muscle for 15 minutes or longer. We concluded that the myoneural junction was the element of greatest susceptibility to heat. The observation was considered sufficiently interesting to publish, and I reviewed the literature in preparation for the writing of the manuscript. I also sought advice from others in the group. At the time, I shared an office with Paul LeFevre, who was then a graduate student and later became well known for his work on red cells. One day he alerted me to a report by Claude Bernard published in Charles Richet's *Dictionnaire de Physiologie* in 1870. Bernard had done essentially the same experiments and come to the same conclusions, except that he had used oil instead of Ringer's solution as the medium. Because the finding had already been made and reported, it was decided not to proceed with publication. How different this attitude was from those prevailing in biomedical science today; now the use of Ringer's solution instead of oil might be considered sufficiently different to justify not only publication but the claim of a significant new discovery. Apropos differences in attitudes between then and now, Heilbrunn once remarked that anyone publishing an average of more than two full papers per year was not doing good work or doing his own work. Today, such a publication rate would probably be considered too meager to merit promotion, tenure, or the acquisition of a grant.

The exposure to scientific research with Heilbrunn caused me to reconsider the study of medicine, and I discussed with him the possibility of my applying to graduate school and seeking a Ph.D. with him. He was willing to accept me but strongly advised me to proceed to medical school. Because of the war, his graduate students were being drafted into the armed forces before achieving their degrees, but medical students were being allowed to complete their studies first. Furthermore, he noted sarcastically that an M.D. degree did not necessarily spoil one for scientific research. I took his advice and applied to the medical school at Penn. Heilbrunn sent a letter of recommendation to the Admissions Committee and told me that whenever he had sent a letter as strong as that one, the applicant was accepted. I was, indeed, admitted to the class beginning in the spring of 1943.

Medical School and Internship

To provide physicians more rapidly for the armed forces, medical schools in the United States adopted an accelerated program in which the full four-year curriculum was compressed into approximately three years. The semester system and vacations were abandoned, and courses followed one another in rapid succession. About three months after entry to the school, the military essentially took over the medical, dental, and veterinary schools. Most of us were inducted into one of the military services, most of us, including me, into the Army Specialized Training Program (ASTP) and a lesser number into the V-12 program of the Navy. Those in the Army were given the rank of Private First Class (PFC); the Navy inductees were treated as cadets. The students in the ASTP at Penn were assigned to barracks, several to a room, improvised in fraternity houses and dormitories of the university. We were trained to be soldiers, for example, to salute and to march, and were instructed in map reading, how to stop tanks, and so forth. We assembled for reveille early each morning and then marched in platoon formations to breakfast at the Palestra, the basketball arena of the university that had been renovated into a gigantic mess hall. That is where we ate all our meals or, more precisely, Army rations. The military did, however, keep hands off the educational process; curriculum and matters of medical education remained fully responsibilities of the university.

There were some benefits to the military take-over. First, the military assumed all the expenses of the medical education and even paid us $54 a month. I, almost certainly, would otherwise never have been able to finish medical school because of our limited financial resources. Secondly, it kept us out of combat, at least for a while; ASTP was sometimes said to stand for "All Safe Till Peace." We were not comfortable with this protected status at a time when our troops were engaged in bloody battles in Europe and the South Pacific, particularly because we were easily recognized by the official shoulder patch of the ASTP that we were required to wear at the top of the left sleeve of our outer garments. The patch was a gold or orange octagon edged by a thin royal blue border. In the middle was a flaming lantern, like Aladdin's lamp, and a vertically oriented sword, the handle pointing downward. Officially it was supposed to symbolize the sword of valor and the lamp of knowledge; we in the medical ASTP referred to it as the catheter and the flaming urinal.

Our first course in medical school was gross anatomy, followed soon afterward by histology and neuroanatomy. At first, I found the atmosphere in medical school intellectually stifling. Compared with the exciting, thought-provoking, problem-solving, and mature atmosphere of Heilbrunn's laboratory, the rigidity of the curriculum and the treatment of the students in medical school seemed more like that in grade school. I could not develop much interest, let alone enthusiasm, in subjects that

required memorization of huge amounts of descriptive, primarily visual information. My mind did not work that way; I was stimulated more by dynamic processes that could be measured and quantified. Nevertheless, I persisted, studied hard, and survived that dull period until eventually we progressed to physiology, biochemistry, and pharmacology; those were more to my liking. All three of those courses were extremely well taught by excellent teachers who often emphasized the research that unearthed the facts being presented. Unlike the present trend in medical schools, each course included hands-on laboratory experiments carried out by the students themselves. The experiments were designed to illustrate important principles. In the lectures, the methods and results of published experiments that had led to the facts being taught were described, interpreted, and critically analyzed. The enthusiasm of many of the teachers for experimental science was transmitted to the students. In physiology Henry Bazett, chairman of the department and a former student of the great physiologist, John Scott Haldane, presented heavily research-oriented lectures on cardiac physiology. He once confessed that he had done experiments on himself in every branch of physiology, except one; he drew the line at experiments involving female sex hormones. Merkel Jacobs, known for his research on diffusion and red cells, taught peripheral circulation. His clear-minded, analytical, rational approach made physiology seem as rigorous and analytical as mathematics. The biochemistry course was almost as stimulating. Most of the lectures were given by David Drabkin, whose enthusiasm was contagious, but excellent lectures were also given by others, for example, Samuel Gurin in lipid biochemistry. Drabkin lectured extensively on the physiological chemistry of diabetes and presented in great detail the procedures and experimental findings that documented the latest concepts about the disease. It seemed to me that if one understood the physiological chemistry of diabetes, one would have mastered most of the biochemistry that existed at that time. One of my most prized possessions is my collection of notes on the lectures on glycolysis by the great Otto Meyerhof, a refugee from Germany and then a professor at the University of Pennsylvania. Pharmacology was probably the best-taught course, mainly as a result of the efforts of an extraordinary trio of teachers, Carl Schmidt, Julius Comroe, and Seymour Kety. They emphasized physiological mechanisms, and the physiology of each system was comprehensively reviewed before the specific actions of drugs were examined. We probably learned as much physiology in pharmacology as in the physiology course. I can still remember Comroe's lecture on cardiac glycosides, a masterpiece of exposition on cardiac rhythms and contractility of heart muscle, Kety's lecture on pain and analgesics, and Schmidt's lectures on respiration and the cerebral circulation. All the lectures laid heavy emphasis on the scientific method and scientific medicine as the basis of rational diagnosis and therapy, and experimental findings were critically present-

ed, evaluated, and interpreted. A healthy skepticism permeated each lecture. For example, in the first lecture of the course, Schmidt warned us not to be seduced by the dictum, "Post hoc, ergot propter hoc." By the end of the course many of us had become therapeutic nihilists.

Most of the other courses in medical school were clinical and less interesting to me. I was clearly stimulated more by basic science than by clinical medicine. I enjoyed neurology because with reasonable knowledge of neuroanatomical pathways and neuropathology one could usually deduce the locations and natures of lesions. Surgery, gynecology, and obstetrics were not intellectually challenging; pediatrics required dealing with children who were always crying and difficult to examine. Of the clinical courses, internal medicine was the most appealing. I found metabolic and endocrine diseases most interesting, probably because they so often involved physiological chemistry. I found nothing in my experience in medical school that would divert me from basic biomedical research to the practice of medicine. My orientation did change, however, from cellular physiology to mammalian physiology and biochemistry.

The war ended in August 1945. A few months later, I graduated from medical school and in March 1946 began my internship at the Philadelphia General Hospital, a city hospital with 2,500 beds. We were discharged from the Army and commissioned in the reserves with the stipulation that we would be recalled to active service as medical officers after we had completed our internships and passed the state board examinations for licensure. Rotating internships were then required in Pennsylvania, and I rotated through internal medicine, tuberculosis service, surgery, orthopedic surgery, clinical laboratory medicine, neurology, psychiatry, obstetrics, and gynecology. Psychiatry was my first rotation, and it was quite an eye-opener. The psychiatric department had about 300 beds in a separate building and functioned mainly as an acute receiving facility. Its responsibility was to observe, diagnose, and treat all treatable patients. Chronic patients not responsive to treatment were transferred to state facilities for long-term custodial care. The treatments we offered were insulin-shock or electroconvulsive therapy for schizophrenia and electroconvulsive therapy for manic-depressive psychosis, involutional melancholia, and reactive depression. Paresis was treated with fever therapy, produced by malaria in whites and by intravenous typhoid vaccine in blacks. Penicillin was not yet available to us. Of course, all patients were given that esoteric, mystical, highly individualized "magic bullet" known as psychotherapy. There were also many admissions with alcoholic hallucinosis, delirium tremens, hysterical paralyses, amnesia, drug intoxication, which at that time was mainly chronic bromidism that bore a remarkable resemblance to schizophrenia, and occasionally brain tumors that presented themselves with psychosis. I must confess that I was intrigued by this incredible world of the mind. The strange and bizarre

behaviors, irrational thoughts, delusions, and hallucinations had to be seen to be believed. They were beyond any comprehension based on physical science but seemed to be real phenomena nonetheless. Psychoanalysis was then in its ascendancy in American psychiatry, and psychiatrists ignored physical and chemical mechanisms. They were fully satisfied with explanations based on early childhood experiences and the id, ego, superego, unconscious mind, and entities in the mind without physical or biochemical structure or properties. Psychiatry was an unknown domain and a challenge to anyone committed to the scientific method and explanations of biological phenomena, even those of the mind, in terms of basic physical and chemical mechanisms.

Internships had been integrated with the accelerated programs of the medical schools during the war, and their duration had been curtailed from the normal one year to nine months. Although the war had ended several months earlier, the accelerated program was still in effect when my internship began, but near its end the one-year internship was reinstated. To do so, it was necessary for scheduling reasons to extend our internship by six months, and we overlapped the next class by three months. The original schedule of rotations still had to be completed during the first nine months, and the additional six months were restricted to a single service. I had already served six weeks in psychiatry, but was assigned to psychiatry for the extra six months. As a result, my internship included almost nine months of neuropsychiatry. Furthermore, immediately after the war's end, many physicians returned from military service seeking specialty training under the G.I. Bill of Rights. Psychiatry was a popular choice, probably because of the nation's concern about the shockingly high rate of rejections from the draft and medical discharges from the services ascribed to psychiatric causes. A commonly heard quip at the time was, "Everyone in this country is psychoneurotic but thee and me, and sometimes I have my doubts about thee." Our hospital became a teaching center in psychiatry for such returning veterans, and classes and clinics were organized to teach them but were open to us as well. When the new class of interns arrived three months before our class finished, they took over the interns' duties, and I was free to attend the training classes and clinics and to serve essentially as a resident in psychiatry. That experience enhanced my knowledge and competence in psychiatry and with it my interest in mental functions.

The Army Years

My internship ended in June 1947. It was during my internship that I married my wife Betty, who was then enrolled in Ohio State University. At completion of her first year, she joined me in Philadelphia just before my internship ended. The Army allowed me two months to take the state

board examination and then ordered me to active duty at the Medical Field Service School, Fort Sam Houston, Texas. There we were given about four weeks of training in basic military medicine. Near the end of the training, a planeload of high-ranking officers arrived from Washington, D.C. and interrogated each of us in the class as to our preferences for subsequent assignments in the Army. They promised to be accommodating, and encouraged us to choose permanent careers in the Army. The representative of the U.S. Army Air Force told us that candidates for flight surgeons had to be smarter than physicians in other branches of the Army because of the complexities of aviation medicine, but on the other hand, they could not be too smart because they would then insist on keeping both feet on the ground. We were given three choices in order of preference for specialty and three more for location. My specialty choices in order were physiological research, internal medicine, and neuropsychiatry. My choices for location were Fort Knox, Tennesse, where there was a major research facility for environmental physiology, followed by the European theater of operations and, finally, the west coast. In typical Army fashion, they granted me my last choice of specialty and a location that I had not selected at all. Because of my experience in neuropsychiatry during internship, the Surgeon General of the Army ordained me a neuropsychiatrist and assigned me to Camp Lee, Virginia.

The medical installation at Camp Lee was a 150-bed station hospital that provided a full complement of medical and surgical services to the Army personnel and their dependents. Before I arrived in the fall of 1947, there had been no psychiatrist there for several months, and neuropsychiatric functions were covered by the Medical Service. My arrival was eagerly awaited, and I was immediately appointed chief of neuropsychiatry. It was left to me to decide whether to keep neuropsychiatry within the Medical Service or restore it to an independent service. Because my interests were still more in internal medicine than in neuropsychiatry, I chose the former so that I could still participate in diagnosis and care of medical patients. It was a wise choice because we saw a variety of interesting medical problems such as cardiovascular and pulmonary diseases, leukemia, and metabolic diseases such as diabetic coma and hepatic insufficiency, in which I was most interested.

Relatively few of my neuropsychiatric patients were neurological, and they were of limited variety because of the restricted age span of the population. Most of them had head, spine, and peripheral nerve injuries, and subarachnoid hemorrhages usually caused by cerebral aneurysms. There was an occasional brain tumor, stroke, or early multiple sclerosis, and one unusual case of dystrophia myotonica. All patients requiring neurosurgical treatment were transferred to Walter Reed General Hospital in Washington, D.C. Psychiatric patients were plentiful, and most were treated as outpatients. There were occasional psychoses that required hospital-

ization; these included schizophrenia, manic-depressive disease, psychotic depression, alcoholic hallucinosis, delirium tremens, and one case of acute amphetamine intoxication. Patients with functional psychoses were either transferred to Walter Reed or else granted medical discharges from the Army. Most of the outpatients suffered from alcoholism, personality disorders, or psychoneuroses, such as anxiety neurosis, hypochondriasis, psychosomatic disorders, and conversion reactions (such as hysterical paralyses and amnesia). Acute situational maladjustments were common in new recruits away from home for the first time, and there were numerous character disorders, mainly constitutional psychopathic inferior (CPI), the nomenclature used at that time for what is now called sociopathic personality. Psychotherapy was all we had to offer the patients, and although I was skeptical of its validity or value, I had the responsibility of doing whatever I could for my patients. I therefore provided a type of psychotherapy that I thought was consistent with the best teaching of the time and within the limits of my own competence. Psychoanalysis was then predominant; it appeared to be the most dynamic school of psychiatry and to offer patients, at least neurotics, the best chance of help. I studied psychiatric texts and journals intensively, read much of Freud's work and that of his disciples, and ended up practicing a sort of diluted, modified version of psychoanalysis. There was no couch; I sat at my desk facing the patient and wrote notes while the patient talked spontaneously or in response to leading questions. Usually at the end of each session, generally once or twice a week, I would offer some interpretative remarks and suggestions. Sometimes I prescribed sedatives and occasionally used amytal interviews (that is, "twilight sleep"), particularly in conversion reactions. Results were probably no better or worse than those obtained by fully qualified psychiatrists at that time. Patients sometimes actually improved. I remember a soldier with a conversion reaction who regained the use of his paralyzed arm, an amnesic who recovered his memory, and a nymphomaniac who gave up sex for Lent. There was one patient who made a particularly strong impression on me. She was in her thirties and had had various systemic symptoms for many years. The internal medical service had studied her thoroughly and could find no organic basis for her complaints; thus, they concluded that she was suffering from psychosomatic disease and referred her to our neuropsychiatric clinic. She certainly exhibited enough psychopathology to make the diagnosis creditable, and I undertook to treat her with my usual type of psychotherapy in two one-hour sessions per week. I often began each session with the question, "How have you been feeling since I last saw you?" On one such occasion after about six months of therapy, she replied, "Wonderful! I haven't felt this well in 11 years."

"You do?" I stammered incredulously, wondering how her talking and my listening could possibly have so altered her brain as to dispel the psychosomatic symptoms. For me, mind and brain were inextricably linked,

a linkage that was irrelevant to psychiatry at that time. This case and others like it stimulated in me a growing interest in physiological and biochemical mechanisms in the brain in mental disease, and I began to consider the possibility of venturing into this field after completing my two years of Army service.

Return to the University of Pennsylvania

In 1948 I learned that S.S. Kety and C.F. Schmidt (1948), my former teachers at Penn, reported the new nitrous oxide method for measuring rates of blood flow and metabolism in the conscious human brain. This method appeared to offer a unique and powerful tool to study the human brain in psychiatric disorders, and I began to entertain thoughts of possibly joining them to learn and to use their method. In August 1949, I left the Army, and my wife and I returned to Philadelphia where my parents lived. My plan was to visit Kety and inquire whether I might possibly work with him, but I procrastinated for several weeks because I really did not think that there was much chance. In fact, I was already contemplating a backup option, completion of clinical training in psychiatry. Many relatively well-paying residencies were still available because of the huge demand for psychiatrists in the post-war era. Finally, I screwed up my courage, went to see Kety in the medical school building at Penn, and learned that he had transferred from Schmidt's Department of Pharmacology to a new Department of Physiology and Pharmacology in the Graduate School of Medicine chaired by Julius Comroe and located in the basement of the same building. After a short wait I was able to see Kety, and I explained to him the purpose of my visit, making it explicitly clear that I was bringing nothing—no skills, no methods, no brilliant research ideas—only a desire to work with him and his group and learn from them as much as I could. It was a fortunate time. He had just been notified that his NIH grant had been approved and funded, and it included support for a still unspecified fellow. Kety pointed out that he had wanted and had set the salary level for someone more experienced and senior than I. He did, however, remember me from medical school and was willing to take a chance with me. Besides, he added, because of my inexperience the stipend would be lower, and perhaps he could use the rest of the allocated salary for a second fellow at my level. I accepted but still had to be interviewed by Chairman Comroe, who would have to approve the appointment. The interview with Comroe occurred about two weeks later, and he did approve the appointment but then immediately asked me about my plans for the future. I was puzzled; we had just agreed that I would come to work in his department.

"I mean your long-term professional goals," he explained. "Will you work here for a year or two before returning to clinical medicine, or do you plan to make a career in physiology?"

I responded that I did not know. On the basis of my past experience I would guess that I would like basic research, but I still did not know how well I would do in it. He replied that he remembered me from medical school, was confident that I would do well, and hoped that I would decide to make a career in physiology. This was very flattering, but before I could express my appreciation, he added, "But not here."

I was stunned and asked, "What did I say wrong? You just said that you thought that I would be suitable for basic research and hoped that I would stay in physiology."

"It's nothing personal," he replied. "It's just that this department has only three people on university salaries, me—Dr. Kety, and Mrs. Sullivan, the department secretary. I am 38 years old and in good health and have no plans to leave. Kety is 35, and as far as I know, he is also in good health and does not plan to leave. And as for Mrs. Sullivan, I don't think you could do her job. Therefore, if you have any thoughts of replacing any of us, forget them. You are here to help us do our research. In return we will teach you how to do research, and if and when you learn it well enough to be able to do your own research, we will be glad to help you to find a place to do it, but somewhere else."

That seemed reasonable to me, and I assented. He then continued, "I may as well tell you now because you will find out anyway. Your salary will be $2,500 per year. Mrs. King, my senior technician, will be making $3,300 per year. That is not a mistake; it is a reflection of the relative worth of the two of you to this department at this time."

That was putting it right on the line, but he had said nothing with which I could disagree. I eventually came to appreciate that his forthrightness and honesty were reflections of his total commitment to physiology and good science. He was constantly challenging us to do our very best and even more. Behind his gruff exterior there was actually a kind, considerate, and generous soul.

Although I had come to work with Kety to study cerebral circulation and metabolism, I was exposed to a much wider experience. The grant from which I was paid was on peripheral circulation to be studied by another method developed by Kety in 1949, the $^{24}Na^{+}$ clearance method. I therefore had to divide my time between cerebral blood flow and muscle blood flow. This was fortunate because the $^{24}Na^{+}$ clearance method introduced me to radioisotopic techniques and forced me to study the physics of radioactivity, which had not been included in my college physics courses. Also, the clearance method was based on the design and mathematical analysis of a kinetic model. I found physiological modeling to be new and fascinating, but my knowledge of mathematics was weak. I therefore made intensive efforts to review and extend my knowledge of mathematics to the point where it was adequate for the problems with which I was dealing. In this I received valuable help from a graduate student, Reuben Copperman, who

had a bachelor's degree in mathematics, a master's degree in theoretical physics, had completed his course work for a Ph.D. in theoretical physics, and had come to our department to do his thesis research in biophysics with Kety. I once again was a student and studied every night until early morning hours. It was not difficult; with an income of $2,500 per year there was little left over to permit many other activities. My wife, who had been a nurse in the Navy during the war, was completing her college education at Penn under the auspices of the G.I. Bill of Rights and could not help financially. Then by 1952 when my salary had been raised to $4,000, our son was born, further straining our financial resources.

Richard Wechsler was Kety's first postdoctoral fellow; I was his second. Wechsler and I overlapped for about a year, and it was from Wechsler that I learned the technical aspects of the procedure of the N_2O method. Both of us learned the theory of the method and the principles of inert gas exchange between blood and tissues directly from Kety, who was then writing his now classic review of the subject (Kety, 1951). As more fellows arrived, Kety's team grew and included Renward Mangold from Switzerland, who studied sleep; Charles Kennedy, a pediatrician who adapted the N_2O method for use in children; Benton King, an anesthesiologist, who worked with Wechsler and me on the effects of norepinephrine and epinephrine on cerebral blood flow (CBF) and cerebral O_2 consumption ($CMRO_2$); and Jerome Kleinerman and Eugene Conners, both of whom worked with us on sleep studies. It was an intellectually active and interactive group. We regularly discussed and analyzed the rationale and results of our studies as well as publications in our immediate fields of interest and in physiology in general. There were various aspects of the overall research program, and we all worked together as a team on each of them as though it were our own project with no detectable rivalry among us. There were no prior decisions and no concerns about who would be first authors on the papers. This was decided by natural selection; each of us gravitated in our reading and thinking selectively to specific aspects of the overall program, and it soon became obvious who was most knowledgeable of the literature and, therefore, best qualified to write the first draft of the manuscript. The author of the first draft became first author. How different the situation then and there was from what exists today. It is only relatively recently that I became aware of rivalries and conflicts among co-workers with regard to order of authorship.

In addition to the scientific interactions within the laboratory, there was also considerable exchange of broader scope among ourselves and with Kety. Kety and his fellows often ate lunch together, usually hamburgers at the Quad Shop, a simple eatery in a dormitory near the medical school. At lunch we generally discussed politics and foreign affairs, news and magazine articles, political science and scientific politics, and science in general. At these lunches, Kety and I sometimes argued about psychiatry. Although I harbored skepticism about formal psychiatric the-

ory and practice, the experience of having had to deal with suffering psychiatric patients and being obligated to try to help them had softened my opposition to psychiatric doctrines. Kety was a "hard-nosed," rigorous, and critical physiologist; he had little regard for the psychiatry of that time, which he considered to be unscientific. I felt compelled to defend it and argued that it was not psychiatry itself that was at fault, but psychiatrists. That was not an original idea. I had read an article by Iago Galdston (1950) in which he compared Freud's impact on psychiatry with the inauguration of the Eiffel Tower at the Paris Exposition in 1889. At the moment of inauguration, a powerful lantern at the top of the tower was turned on and directed downward; it produced a giant circle of intense light on the ground below. It was night, and those who were outside the circle were in the dark and could see nothing, but those who were within the circle of light were so blinded by its brilliance that they also could see nothing. I too believed that many psychiatrists and disciples of Freud had interpreted and extrapolated too far and had exceeded the bounds of logic and reason, let alone scientific rigor. In our arguments about psychiatry, both Kety and I must have been persuasive because I eventually gravitated deeper into basic science while Kety drifted toward psychiatry with his studies on the genetics of schizophrenia.

The staff of the Department of Physiology and Pharmacology was outstanding and provided a superb environment for training in physiology. Contact between fellows and staff was continuous and close, and expectations and standards of performance were high. There was little tolerance for pomposity or verbal gymnastics. It was not safe to open one's mouth without knowing precisely what one was talking about. The weekly department seminars were held on Saturday mornings, and each professional member of the department was scheduled to present his work. There were no excuses, even if the work was not yet ready for presentation; that itself might be revealing. These seminars were to the fellows what the Roman Coliseum must have been to the Christians; it was like being fed to the lions. Every statement might be challenged and questioned. Every method or conclusion could be criticized. The speakers were usually stretched to the limits of their knowledge of the subject that they were presenting. One dared not make a rash statement that could not be backed up by facts or reason. We learned to be as critical of our own work as we were of the work of others, an attitude that has remained with me and has stood me in good stead. In science it is more important never to be wrong than ever to be right. The scientific literature should never be polluted with the results of bad science. A corollary of this attitude, of course, is that we expect others to be as critical of their work as we are of our own, an expectation that is becoming increasingly more unrealistic. It seems nowadays that many consider it more important for publications to contribute to bibliographies than to scientific knowledge.

The first research project on which I had been designated as the first author was on the effects of hyperthyroidism on CBF and $CMRO_2$ in man. The objective was to find a condition in which energy metabolism in brain was increased. After its development, the N_2O method had been applied to many clinical conditions. In all cases in which consciousness was depressed (such as diabetic acidosis and coma, hepatic coma, renal failure, brain tumors, anesthesia, and so on), O_2 consumption of the brain was decreased, but no conditions had yet been found in which $CMRO_2$ had been increased. We speculated that hyperthyroidism might be a condition in which $CMRO_2$ would be increased, partly because of the marked anxiety suffered by these patients and, even more so, because of the large increase in their total body metabolic rate. We had carefully designed a long-term study in which patients with Graves' disease would be studied not only before and after treatment but also in comparison with normal subjects of comparable age. In the first few experiments it became obvious that, contrary to expectations, $CMRO_2$ remained normal in hyperthyroidism. A few months later, an abstract was published by others reporting the major finding: no change in $CMRO_2$ in human hyperthyroidism. We had been scooped. Indicative of the scientific attitude of our group and probably of many others at that time, Kety consoled me by saying, "Don't feel bad. It must not have been such a great idea. Somebody else thought of it too." It was a time when scientists were valued more for their uniqueness than for their speed.

We did eventually complete the study (Sokoloff et al., 1953), but by then I had become intrigued by the question of why the brain failed to participate in the body's general increase in metabolic rate in hyperthyroidism. What was different about the brain's biochemistry from that of other organs? I searched the literature back to the end of the 19th century when thyroid diseases were first recognized and thyroid physiology began to evolve. It became obvious that we still did not know why thyroid hormones stimulated metabolic rate in those tissues that did respond to thyroid hormones, such as liver, muscle, and kidney. How could we then explain why these hormones did not have the same effects in brain tissue? From the review of the literature, it appeared to me that thyroid hormones must have some special influence on protein metabolism. The mature brain was known to derive almost all of its energy from the oxidation of glucose. The testis was the only organ other than the brain known to have a respiratory quotient of one, indicating oxidation of only carbohydrate, and it too was reported to have a rate of O_2 consumption that was unaffected by thyroid hormones. It might have been coincidence, but it also suggested that thyroid hormones might be acting primarily on protein metabolism and only secondarily on energy metabolism, and their effects might, therefore, not be apparent in organs with low rates of protein turnover as compared to those of carbohydrate. The question

remained whether it was protein synthesis, protein catabolism, or both that were affected. The fact that thyroid hormones did stimulate energy metabolism and was required for normal growth and maturation in developing brain suggested an effect at least on protein synthesis. The mature brain has relatively low rates of protein synthesis and turnover and should be expected to be relatively insensitive to thyroid hormones.

This was our hypothesis, and to test it would require examination of the effects of thyroid hormones on protein synthesis. There was, however, no practical method for studying protein synthesis *in vivo* at the time, and biochemical experiments *in vitro* would be required. I had a fair knowledge of biochemistry from extensive reading and continual discussions with my biochemical colleagues, but I was not a biochemist and not trained in laboratory biochemical techniques. Instead, I tried to persuade biochemists to undertake such studies. One biochemist with whom I often discussed the problem was Beryl D. Polis, a close friend from whom I learned a great deal of biochemistry. He was one of Otto Meyerhof's only two Ph.D. students in America. Polis had previously collaborated with Kety on studies of diabetic coma (Kety et al., 1948) and had remained closely associated with Kety's group. Polis encouraged me to undertake the biochemical studies myself and assured me that with his guidance I could do so. I was, however, too busy with other projects on cerebral and peripheral blood flow and metabolism to undertake such studies.

The Years at the National Institute of Mental Health

In 1951, about two years after I joined him, Kety left Penn to become the first scientific director of the combined Intramural Research Programs of the National Institute of Mental Health (NIMH) and the National Institute of Neurological Diseases and Blindness (NINDB). Because I had become the most senior member of his group, it became my responsibility to continue the research projects that had been initiated by him. He returned almost every other Saturday to discuss our progress. Our department had two major programs: pulmonary function, which was Comroe's chief interest, and cerebral circulation and metabolism, which were Kety's interests. After Kety left, however, his group withered because it lacked a magnet to attract fellows and investigators. We were reduced to the graduate student, R. Copperman, one technician, and me, and I began to feel quite isolated. Comroe invited me to join his group in respiratory physiology, but despite their high quality and the challenging problems that they were investigating, I could not develop any great enthusiasm for studying lungs rather than brain. I therefore began to explore opportunities elsewhere. At the time I was collaborating with the Aviation Medical Acceleration Laboratory of the U.S. Naval Air Development Center in Johnsville, Pennsylvania, to develop a method for rapid continuous measurement of cerebral blood flow and metabolism in man; the Navy want-

ed such a method to study blackout in aviators pulling out of dives. The laboratory's scientific director offered me the position of head of physiology, and it was an attractive offer, particularly since Polis had gone there as head of biochemistry. Comroe, however, strongly objected to my taking that position; he thought it was a bad choice for my career and tried to dissuade me. After I explained my reasons for wishing to leave his department, he called Kety at NIH and suggested that he talk to me. Kety then called me and invited me to join him at the NIMH. He explained that he had not invited me previously because he had not wished to raid the department at Penn when he left. I accepted, and in December 1953, arrived at the NIMH. The Intramural Research Program of the NIMH had a basic science division and a clinical division. Because of my past experience, I could choose appointment in either division. The clinical program a higher grade and salary, I chose basic science.

My position was in the section on Cerebral Metabolism of the Laboratory of Neurochemistry. Kety was both the section chief and the acting chief of the laboratory until a permanent laboratory chief was recruited. There were two other sections in the laboratory: the section on Lipid Chemistry, headed by Roscoe Brady, and the section on Physical Chemistry, led by Alex Rich. The Intramural Research Program of the NIMH also contained the Laboratory of Cellular Pharmacology, in reality a biochemical laboratory, directed by Giulio Cantoni, the discoverer of the methionine-activating enzyme and S-adenosylmethionine and their roles in methylation reactions. Another member of this laboratory was Seymour Kaufman, who had identified succinylCoA as an intermediate in the conversion of α-ketoglutarate to succinate in the tricarboxylic acid cycle and had characterized the role of this intermediate in substrate phosphorylation. Biochemistry was, therefore, well represented, and a biochemical journal club was organized in which we all took turns presenting. In the first cycle each of us presented research we had done before coming to NIH. I presented my work with thyroid hormones, including my extensive review of the literature, and ended with my hypothesis that many of the physiological effects of thyroid hormones could be explained by a stimulation of protein synthesis and turnover. The hypothesis stimulated considerable interest and discussion, and the session lasted well beyond its scheduled one hour. Shortly thereafter, Kaufman came to see me and said that he found the hypothesis to be attractive; in fact, he had come to a similar conclusion from an entirely different perspective. He then asked what I intended to do about it. Once again, I pointed out that the problem was biochemical and that, though I might have sounded like a biochemist....I really was not. He then offered to collaborate with me, provide the biochemical expertise, and supervise and train me in biochemistry. It was also convenient because our laboratories were just around the corner from each other. I enthusiastically accepted his offer, and thus began my career in biochemistry.

With Kety's encouragement, Kaufman and I initiated our experiments in 1955 to develop and characterize an appropriate assay system for protein

synthesis that could be used to examine the effects of thyroid hormones. Progress was slow because both of us had to devote time to other projects to which we were already committed, in my case the studies of cerebral circulation and metabolism. We eventually did develop a satisfactory assay system and found that thyroid hormones did, indeed, stimulate protein synthesis (Sokoloff and Kaufman, 1959, 1961). Kaufman turned out to be an outstanding teacher. He was knowledgeable, scholarly, and rigorous with uncompromisingly high standards. His attitudes and mine meshed perfectly; we shared the same commitments to the traditional values of science. This experience and the capability that biochemistry seemed to offer for definitive solutions seduced me away from physiology and, in 1959 when my projects on CBF were essentially completed, I turned my efforts fully to biochemical research. My main research project was still on the mechanisms of actions of thyroid hormones, but my interests broadened and became oriented generally toward relationships between biochemical processes and physiological functions, particularly in the nervous system.

When I arrived at the NIMH, my first goal was to continue studies of cerebral blood flow and metabolism in man in conditions with normal and abnormal mental and neurological functions. I therefore set up the Kety/Schmidt nitrous oxide method and used it to study normal aging and dementia (Dastur et al., 1963) and the effects of LSD in normal subjects and schizophrenic patients (Sokoloff et al., 1957). The N_2O method measured average blood flow and metabolism in the brain as a whole; this was sufficient to provide much of our present knowledge of the physiology and pharmacology of the cerebral circulation and to demonstrate decreases in cerebral energy metabolism in disorders associated with depressed levels of consciousness or dementia. It did not, however, reveal changes in cerebral energy metabolism during physiological alterations in mental function or in functional psychoses. For example, no changes in $CMRO_2$ were found during mental exercise (that is performance of mental arithmetic), slow-wave sleep, sedation or tranquilization, schizophrenia, mild alcoholic inebriation, or LSD intoxication. There were at least three possible explanations for these negative results: (1) altered mental functions not associated with altered levels of consciousness are unrelated to changes in cerebral energy metabolism; (2) there are changes in local metabolic rates, some increases and some decreases, which are distributed throughout the brain without affecting the average metabolic rate of the brain as a whole; (3) the regions of the brain involved in specific mental changes are too small and localized to be detected in measurements of average metabolic rate in the brain as a whole. We leaned toward the latter two possibilities because of evidence obtained in other tissues, such as heart, skeletal muscle, and kidney, that energy metabolism and functional activity of the tissue are closely correlated. What was clearly needed was a method to measure local cerebral metabolic rates that could be used in conscious animals in various functional states.

There was then no obvious way to measure local metabolic rates in the brains of unanesthetized, conscious, behaving animals, but Kety (1951), in his conceptualization of the principles of inert gas exchange between blood and tissues, had derived an equation that suggested an approach to the measurement of local CBF. Blood flow is, of course, not metabolic rate, but under most normal circumstances local blood flow can be expected to adjust to and, therefore, indicate local energy metabolism. The development of such a method was initiated by Kety and two neurophysiologists, William Landau and Walter Freygang, shortly after Kety's arrival at NIH. When I arrived in 1953, I joined the team to aid in the development of this method. The outcome was the [^{131}I]trifluoroiodomethane ([^{131}I]CF_3I) method (Landau et al., 1955; Freygang and Sokoloff, 1958; Kety, 1960). This method was applicable to conscious animals and measured local rates of blood flow simultaneously in every region of the entire nervous system. A unique feature of the method was its use of a quantitative autoradiographic technique that was developed specifically to achieve the anatomical resolution of the method and to provide visual images of the distribution of the relative rates of local blood flow in the brain. Applications of this method proved unequivocally that local cerebral blood flow does change with local neural activity. For example, it showed that retinal stimulation with light flashes stimulates blood flow in all components of the visual system of the cat (Sokoloff, 1961); to my knowledge this was the first example of imaging of local cerebral functional activity.

Although the quantitative autoradiographic technique was initially designed for ^{131}I, it was obvious that it could be adapted for use with other isotopes, such as ^{14}C, which would be more appropriate for studies of metabolism. Local energy metabolism could be more specifically related to local functional activity than blood flow, which was believed to be only secondarily adjusted to metabolic demand and was known to be sensitive to factors other than local tissue metabolism, such as pCO_2, pO_2, and pH of the arterial blood. In 1955 to 1956 I tried to develop a kinetic model for a method to measure local cerebral glucose utilization ($1CMR_{glc}$) which used [^{14}C]glucose as the substrate and took advantage of the spatial localization provided by the quantitative autoradiographic technique. It soon became apparent that the early loss of labeled products of [^{14}C]glucose metabolism, mainly $^{14}CO_2$ and possibly lactate and other metabolites, would necessitate extremely short experimental periods to minimize significant loss of product. With such short periods, however, the time-integrated specific activities of the precursor pools of glucose in the local cerebral tissues, which had to be known, could not be accurately determined from measurements in blood or plasma because of the lag of the tissue pools behind that of the plasma. I therefore abandoned the project.

In 1957, I was preparing a chapter on energy metabolism in the central nervous system *in vivo* for the *Handbook of Physiology* and, in discussions about it with Donald Tower, I learned about a compound, 2-deoxyglucose

(DG), which in pharmacological doses produced a comatose state that was indistinguishable from hypoglycemic coma even though it also caused hyperglycemia. The mechanism of its effect was unknown. Earlier studies by Sols and Crane (1954) had shown that 2-DG could be phosphorylated just like glucose by hexokinase, but its product, 2-DG-6-phosphate (DG-6-P), could not be isomerized to fructose-6-phosphate (F-6-P), the next step in the glycolytic pathway, because of the lack of a hydroxyl group on its second carbon. Subsequent studies by several groups indicated that DG-6-P could competitively inhibit the conversion of glucose-6-phosphate (G-6-P) to F-6-P. DG appeared to produce coma by blocking glycolysis and, therefore, glucose utilization in brain. The glycolytic blockade, however, was not attributable to competitive inhibition of the transport of glucose across the blood-brain barrier or its phosphorylation by hexokinase because glucose concentrations in blood and brain tissue are relatively high. The blockade resulted from accumulation of DG-6-P to concentrations eventually exceeding those of G-6-P in the cells; the DG-6-P then competed with G-6-P for the enzyme glucose-6-isomerase, and blocked its conversion to F-6-P and, therefore, glycolysis. DG-6-P could accumulate in brain to such relatively high levels because it was a poor substrate for most enzymes in brain that might metabolize it, and also because glucose-6-phosphatase (G-6-Pase) activity was low in brain tissue (Hers, 1957). When this picture emerged, it occurred to me that radioactive DG in tracer amounts might be used to measure local cerebral glucose utilization by the autoradiographic technique. The development of an operational method would, however, require considerable time and effort, and I was then too deeply engaged in studies on the actions of thyroid hormones to undertake it. I filed the idea away as something for future work but did make use of the properties of DG in biochemical experiments *in vitro*. For example, in studies of oxidative phosphorylation by crude brain mitochondria, we had to use a combination of glucose and hexokinase to trap the generated ATP to protect it from the high levels of ATPase activity in the preparations. Crude brain mitochondrial preparations, however, contained glycolytic enzymes that metabolize the G-6-P formed by the trap and generate additional ATP above that produced by oxidative phosphorylation. I therefore used DG instead of glucose in the trapping system, and this solved the problem. The DG-6-P, once formed, was neither hydrolyzed to release inorganic phosphate nor metabolized further to generate additional ATP.

In 1963 William Windle, chief of the Laboratory of Perinatal Physiology, NINDB, invited Kety, Charles Kennedy, and me to his laboratory in San Juan, Puerto Rico, to study local CBF in fetal and newborn monkeys. There were major obstacles to the use of $[^{131}I]CF_3I$ in these studies. Because the compound was not commercially available and ^{131}I has a half-life of eight days, it would have been necessary for us to spend half of our time on its synthesis. Furthermore, it was a radioactive gas, and spe-

cial facilities needed to synthesize and handle radioactive gases were not available in the San Juan laboratory. We decided, therefore, to modify the [^{131}I]CF_3I method for use with a nonvolatile tracer labeled with a longer-lived isotope, one with low energy ß-radiation, such as ^{14}C, that would allow better autoradiographic resolution. First we tried [^{14}C]thiopental, which would have been suitable except for the inconvenience of its widely different tissue-blood partition coefficients in the various structures of the brain. [^{14}C]antipyrine appeared to be a better choice because of its uniform brain:blood partition coefficient throughout the brain. In 1964, Martin Reivich and Jane Jehle joined our laboratory, and by 1965 they had modified the quantitative autoradiographic technique and the [^{131}I]CF_3I method for use with [^{14}C]antipyrine (Reivich et al., 1969). [^{14}C]antipyrine was later found to diffuse too slowly across the blood-brain barrier and was replaced by the more freely diffusible [^{14}C]iodoantipyrine (Sakurada et al., 1978). Now that quantitative autoradiography with ^{14}C was available, the idea of measuring local cerebral glucose utilization with [^{14}C]DG was resurrected. Kety, Reivich, and I frequently discussed this possibility but again left it for the future.

Reivich left NIMH in 1966 and returned to the University of Pennsylvania. In 1967 he called me and asked if I was still interested in DG and willing to undertake a collaboration with him to develop the method for measurement of local cerebral glucose utilization with [^{14}C]DG. I accepted the collaboration but pointed out that commitments of my own laboratory to other projects made it temporarily impossible for any of the experimental work to be done there; the experiments would have to be done in his laboratory. He agreed, and the project began. The initial studies were carried out with brain slices *in vitro* and demonstrated that [^{14}C]DG and glucose were taken up from the incubation medium in proportionate amounts. These results encouraged us to design a model that was essentially the same as that for the local blood flow method, except that it included a metabolic trap for the tracer in the tissue. An equation was derived which would allow the calculation of local glucose utilization, provided that local blood flow and other factors which were difficult to determine, were also known. This early attempt was reported in 1971 (Reivich et al., 1971). The model was not wrong, but the operational equation derived from it required information that was difficult if not impossible to obtain. The project then stagnated.

In 1968 I became aware that if I were ever to take a sabbatical year, it would have to be then and I interrupted my research at NIH to spend a year in Jean Roche's Laboratory of General and Comparative Biochemistry at the Collége de France in Paris. There I worked with Jacques Nunez and Jacques Pommier in studies of peroxidase-catalyzed iodination of proteins. We used horseradish peroxidase, radioactive iodide, and serum albumin or lysozyme in a reaction that was a model for the iodination of thyroglobulin

in the pathway of thyroid hormone biosynthesis in the thyroid gland. This reaction exhibited unusual kinetics that intrigued me (Pommier et al., 1973). Because of my previous experience in the design and mathematical analysis of physiological models, enzyme kinetics always attracted me. While working on the kinetics of this reaction in Paris, I developed considerable facility with enzyme kinetics. It was then that it occurred to me that a new model based more on enzyme kinetic principles than on only blood flow and principles of tissue-blood exchange might be more productive in the development of the [^{14}C]DG method.

When I returned to NIH in September 1969, I found the project in my laboratory on the action of thyroid hormones to be in shambles. I could try to resurrect it or take advantage of the opportunity to introduce a new project, and I chose the latter. After a period of reorganization of the laboratory, I initiated the development and mathematical analysis of a new enzyme kinetic model for the autoradiographic DG method for measuring local cerebral glucose utilization. The first animal experiment was carried out in February 1971 by Charles Kennedy, Michael Des Rosiers, Jane Jehle, and myself. Soon after, Clifford Patlak, Karen Pettigrew, Osamv Sakurada, and Mami Shinohara were added to the team. All played unique and important roles, and progress was relatively rapid. The method was fully developed for use in rats in about three years and formally presented for the first time at the meeting of the American Society for Neurochemistry in New Orleans, March 1974. It took two more years to complete the experiments needed to adapt the method for use in monkeys.

At first we did not know if local energy metabolism was linked to local functional activity in nervous tissues as in other tissues, and if it was, whether the DG method could localize regions of altered functional activity on the basis of altered metabolism. We therefore embarked on a series of studies that were largely exercises in neurophysiology but were equivalent to what biochemists call "recovery experiments." Specific regions in the nervous system were functionally activated or depressed by conventional physiological procedures, and the [^{14}C]DG method was applied to determine if we could recover changes in $1CMR_{glc}$ in the appropriate regions. The results of such studies in auditory, visual, and motor systems provided unequivocal evidence of the linkage between local functional activity and energy metabolism in the nervous system. The effects of altered functional activity on $1CMR_{glc}$ were often so pronounced that they could be visualized directly in the autoradiograms without the need for quantification. A particularly dramatic example was the visualization of the nature, extent, and distribution of the ocular dominance columns and the loci of the representation of the blind spots of the visual fields in the striate cortex of the monkey. These results were published as examples of the usefulness of the method for mapping functional neuroanatomical pathways even without quantification (Kennedy et al., 1975, 1976). Full

and detailed descriptions of the theory and procedure of the fully quantitative method and the results obtained with it were published later (Sokoloff et al., 1977; Sokoloff, 1977, 1981, 1982).

The quantitative [^{14}C]DG method yielded massive amounts of data. It required manual densitometric analysis of the autoradiograms, which was tedious, laborious, and, therefore, limited to relatively few selected structures. Valuable information contained in the autoradiograms was being lost when the data were organized and presented in tabular form. A means to combine the quantitative strength of the method with the spatial resolution of the autoradiograms was needed. Therefore, in collaboration with Wayne Rasband, a computer scientist at the NIMH, we assembled a computerized image-processing system that scanned and digitized the autoradiograms, computed 1CMR$_{glc}$ for each pixel, and reconstructed on a monitor the autoradiographic images in pseudocolor with the metabolic rates quantitatively encoded in color in accordance with a calibrated color scale that was simultaneously displayed. Charles Goochee, a chemist in our laboratory, developed the computer program (Goochee et al., 1980). This technique facilitated rapid, quantitative survey of the entire nervous system for regions with altered rates of glucose utilization. It also provided dramatic quantitative metabolic maps of the nervous system in various functional states in which regions of altered activity were easily visualized by the color changes. Such color-coded metabolic maps were first presented at the annual meeting of the Society of Neuroscience in St. Louis, Montana in 1978, by Charlene Jarvis, who used them to illustrate the local metabolic consequences of visual deprivation of one hemisphere in the monkey observed in collaborative studies between our laboratory and Mort Mishkin's Laboratory of Neuropsychology at the NIMH. They caused a sensation. In fact, the issue of *Chemical & Engineering News,* which reported on the meeting, featured on its cover a color-coded autoradiograph of the striate cortex showing the markedly reduced metabolism in the deprived hemisphere, with the caption "Visualizing Brain Chemistry in Action."

Shortly after the [^{14}C]DG method was developed, Reivich urged that we undertake its adaptation for use in humans. The theoretical basis of the method was fully applicable to humans, but autoradiography could not be used to measure tracer concentrations in localized regions of brain tissue. A noninvasive technique for measuring local tissue concentrations of isotope by external detection was needed. David Kuhl, then in the Department of Radiology at the University of Pennsylvania, had previously constructed a section scanner that could measure local concentrations of γ-emitting isotopes in cross-sections of human brain by external scintillation counting. Reivich brought him into the project. Another problem was the introduction of a γ-emitting isotope into the deoxyglucose molecule to allow external detection of the radioactivity. Deoxyglucose contains only hydrogen, oxygen, and carbon, but there are no γ-emitting isotopes of

hydrogen, and the γ-emitting isotopes of oxygen and carbon, ^{15}O and ^{11}C, have half-lives of 2 and 20 minutes, respectively, much too short for radiochemists at that time to be able to synthesize deoxyglucose labeled with them. An alternative possibility was to use a fluorinated derivative of deoxyglucose, one labeled with ^{18}F, a positron-emitting isotope with a half-life of 110 minutes. Because fluorine is so small an atom, metabolic substrates fluorinated in appropriate positions in the molecule often retain biochemical properties of the natural compound. Alfred Wolf, a radiochemist at Brookhaven National Laboratory, was brought into the project, and he and his team developed a rapid synthesis of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG). Initial experiments carried out in our laboratory at NIMH with 2-[^{14}C]FDG demonstrated that the fluorinated derivative retained the essential biochemical properties of deoxyglucose. Soon afterward, the [^{18}F]FDG adaptation of the DG method was developed and used for the first time in humans with Kuhl's Mark IV Section Scanner (Reivich et al., 1979). Shortly thereafter, Kuhl moved to UCLA with two of his coworkers, Michael Phelps and Edward Hoffman, both pioneers in the design and use of positron-emission tomographic instruments. Positron-emission tomography (PET) offered better spatial resolution and accuracy than Kuhl's single photon scanner. ^{18}F is a positron-emitter and its γ-radiation consists of 0.51 MEV annihilation γ-rays produced when positrons are absorbed in matter. The group at UCLA acquired a PET scanner and adapted the [^{18}F]FDG technique for use with PET (Phelps et al., 1979). They and many others around the world have used the [^{18}F]FDG technique with PET to study the human brain in a variety of nervous and mental diseases; the technique is also used extensively to study coronary artery insufficiency. It is the method that first demonstrated the usefulness of PET to study local metabolism and function in the human brain.

The [^{14}C]deoxyglucose method was warmly received at first, and I was awarded several prestigious honors for it. I was therefore unprepared for the controversy that soon engulfed it. In our development of the method we were acutely aware that glucose-6-Pase activity, if present in brain, could present problems, namely loss of labeled product and therefore underestimation of $1CMR_{glc}$. We therefore took pains to assure ourselves that effects of G-6-Pase activity were negligible. We scrupulously studied the effects of time following administration of [^{14}C]DG on the estimates of $1CMR_{glc}$; any effects of G-6-Pase activity would be time dependent and become more prominent with increasing time. The results showed no significant effects with experimental periods less than 60 minutes, and we therefore adopted 45 minutes as the standard and maximal permitted length of the experimental period in rats and monkeys. The initial report of the method in 1977 (Sokoloff et al., 1977) presented the results that showed no significant differences in estimates of $1CMR_{glc}$ obtained with 30 and 45 minute experimental periods. Nevertheless, an extended argu-

ment developed about whether the DG method was invalid because of effects of G-6-Pase activity. It began with a report by Hawkins and Miller (1978) that purported to show loss of more than 50 percent of [^{14}C]DG-6-P due to G-6-Pase activity in brain tissue. They measured brain [^{14}C]DG-6-P content directly and compared it with the predicted amount calculated with a transposed version of the operational equation of the DG method that assumes no loss. This equation contains a combination of kinetic constants, named the "lumped constant," which we had measured and reported in our initial paper. Hawkins and Miller used a value more than twice its measured value, and this, not G-6-Pase activity, was responsible for the discrepancy between their measured and calculated values for brain [^{14}C]DG-6-P content (Sokoloff, 1982). Their error arose indirectly from the fact that their measured and calculated time courses of [^{14}C]DG-6-P content were for the whole brain, but the operational equation of the DG method on which the calculated values were based applies only to tissues that are homogeneous with respect to rates of blood flow, metabolism, transport, tracer concentrations, and so forth, a requirement not met in the heterogeneous mixtures of tissues in the whole brain (Nelson et al., 1987; Schmidt et al., 1991, 1992).

Before this issue was resolved, Huang and Veech (1982) reported that when a mixture of glucose uniformly labeled with ^{14}C ([U-^{14}C]glucose) and glucose labeled in the 2-carbon position with tritium ([2-^{3}H]glucose) was presented to the brain, the pool of glucose in the brain lost its ^{3}H more rapidly than its ^{14}C. Their explanation for this phenomenon was that both species of labeled glucose were phosphorylated at equal rates to G-6-P and then isomerized to fructose-6-phosphate, a reaction in which the ^{3}H on the 2-carbon would be lost but the ^{14}C retained. The isomerase reaction is reversible, and G-6-P without the ^{3}H but with the ^{14}C would be regenerated. Then, and only then, if there were G-6-Pase activity in the brain, the labeled G-6-P would be hydrolyzed back to free glucose without the ^{3}H but with its ^{14}C. Although widely accepted at first, their explanation also turned out to be wrong. Tom Nelson, Gerald Dienel, and Nancy Cruz in our laboratory were able to reproduce the findings of Huang and Veech when they used the same procedures that Huang and Veech had used. When they used a more thorough and rigorous procedure to isolate the free glucose from the brain, however, then no differential loss of ^{3}H and ^{14}C was observed (Nelson et al., 1985; Dienel et al. 1988). It took them several years to examine critically all the steps in the procedures used by Huang and Veech and to pinpoint the sources of error in their study. There were a number of errors, the most important of which was the presence of labeled impurities in the glucose fraction that they had isolated and presumed to be pure; only 40 percent of the total ^{14}C in their so-called glucose fraction was in glucose. The fraction contained at least six other labeled contaminants, mainly ^{14}C-labeled products of glucose metabolism

beyond the fructose-6-phosphate step that would have lost the ^{3}H but not the ^{14}C. The effort required to find the sources of these errors was a major detour from and damaging to the overall research program of the laboratory, but it was necessary to resolve the controversy. In a multidisciplinary field like neuroscience, there were many who used the DG method without being adequately educated in the basic principles to comprehend the biochemical and physiological intricacies of the issue; they knew only that there was a controversy, and that was enough for them to be skeptical. They would not be convinced until the exact sources and nature of the errors made by those who raised the issue in the first place were identified and proved. It took most of a decade to do this, but it was necessary to save the DG method from unwarranted extinction (Nelson et al., 1985, 1986, 1987; Dienel et al., 1988, 1990).

It is gratifying to note that the methods that have come out of the basic physiological and biochemical research of our laboratory have led to the birth and growth of essentially a new field, perhaps, even an industry, in neuroscience: the field of functional brain imaging. When we first started, we did not know for certain if there was any relationship between local functional activity and local blood flow and/or energy metabolism in the nervous system. Methods to determine this were not available, and we had to develop methods to measure local blood flow and metabolism in the unanesthetized brain. These new methods also made it possible to examine blood flow and metabolism not only in selected regions but simultaneously in all regions of the brain. With these methods, we were able to establish that local blood flow and energy metabolism are, indeed, linked to local functional activity and can be used to map regions of altered functional activity in the brain. The development of new technology, like PET, made it possible to adapt these methods for use in humans. It is exciting to know that their applications may provide valuable information about normal brain function and its abnormal function in neurological and mental disorders.

Reflections on Then and Now

I would be remiss if, with the perspective of more than 45 years in biomedical scientific research, I failed to comment on the changes that have occurred in the state of the biological sciences today. Certainly the most striking and important changes have been in the vast expansion of our fundamental biological knowledge as well as the technology that made it possible and continue to support it. The material support supplied by industry in the form of equipment, apparatus, chemicals, enzymes, kits, and so forth is incredible; scientists can now concentrate on the experiments that answer biological questions rather than on the preparation of materials and tools needed for the experiment. Little time needs to be spent on synthesis of compounds, enzyme purification, assembly of appa-

ratus, and so on. The pace has accelerated, and knowledge is flowing in at an explosive rate as witnessed by the proliferation of new periodicals and the growing size of the established journals. Concomitantly, computerized techniques to access and manage all this information are becoming ever more available and sophisticated. It would seem to be a wonderful time for science, but I wonder if is equally good for scientists. It reminds me of the slogan in the cigarette advertisement shortly after filtered cigarettes became fashionable, "Are you smoking more and enjoying it less?"

When I first entered my scientific career, research was almost purely an academic pursuit, at least in research-minded universities. It was supported largely to advance knowledge for the sake of knowledge and also to educate and train the next generation of scientists. Life in scientific research was, in truth, like that in an ivory tower or monastery where we could leisurely ruminate, discuss and debate with our colleagues, and enjoy the process of inquiry and learning. Indeed, the process of research was itself almost as enjoyable as the discovery. When I returned to Penn after my Army service, I was paid from an NIH grant but Kety himself received no salary from the grant. The NIH policy then was that principal investigators could receive no salaries from their own grants, and the maximum overhead was 15 percent. Principal investigators were, therefore, individuals who had already been evaluated and selected by their institutions for salaried positions; their grants provided salaries for fellows and support staff. The rationale, I suppose, was that it was to the nation's advantage to support scientific research conceived and initiated by already-qualified faculty members, provided, of course, that the proposed research was subjected to peer review and deemed worthwhile. Some time late in the Eisenhower or early in the Kennedy administration (I do not recall which) the policy changed: principal investigators were allowed to receive salaries in proportion to their time on the project, and the limit on overhead was removed and made negotiable. Universities and other institutions were quick to take advantage of this golden egg. Faculties and departments expanded, and everyone was expected to apply for grants as soon as possible. Fellows were rushed through their postdoctoral training to achieve so-called independence, an absolute requirement for tenure. Independence no longer necessarily means true scientific or intellectual independence; it means having one's own grant support. The result is that we have a multitude of well-trained and not so well-trained scientists competing for funds that are growing but cannot possibly keep pace with the growth in the number of grant applications. Many grant applications fail, and the applicants, whose salaries and appointments depend on grants, spend more and more of their time preparing grant proposals and less and less on research and training of the new scientists. Indeed, they often misuse their fellows in their pursuit of grants. Because in most institutions one needs a grant to have a salary, research proposals are often contrived more to get money than to advance knowledge. At scientific meetings,

the corridor and dinner conversations are almost entirely about grant seeking rather than the substance of science.

Such was not the case when I was a fellow. Fellows could then devote all of their time exclusively to research and study, and they could continue to be supported by grants of senior investigators for extended periods of time until they became truly mature scientists. The search for money to support the research was the responsibility of the principal investigators who had an institutional salary and could develop grant proposals based on good scientific questions rather than on criteria deemed most likely to obtain a funded grant. New researchers had time to develop under the umbrellas of senior scientists who usually found their disciples positions elsewhere when they were ready. The net result is, as I see it, that biomedical research is now less an academic and scholarly pursuit and more like a commercial or industrial endeavor. Indeed, the influence of industry has already made an impact on the climate of biomedical research, and I fear that the academic environment will eventually suffer as a result. The current atmosphere in biomedical research is such that if it had been so when I made my choice, I might well not have chosen it.

Selected Publications

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