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Marcus E. Raichle, Sr.

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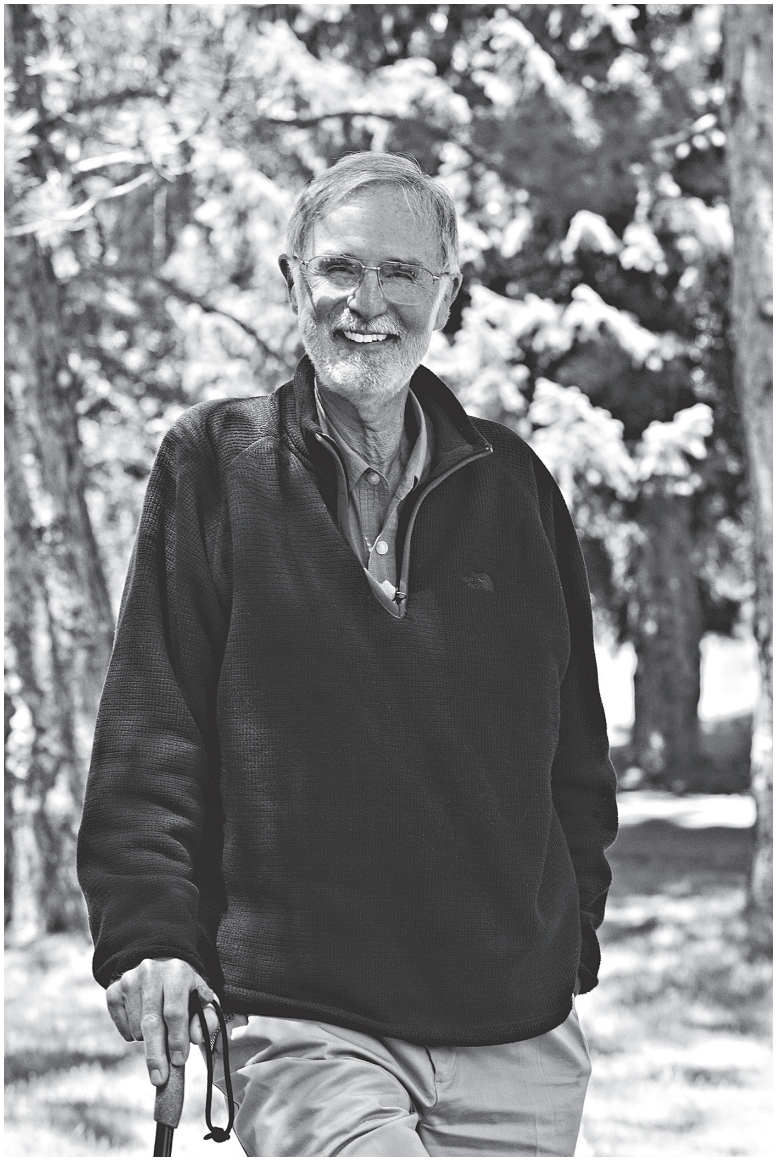

Marcus E. Raichle, Sr.

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March 15, 1937

Education:
University of Washington, BS (1960)
University of Washington, MD (1964)

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Intern and Resident, Medicine, Baltimore City Hospitals (1964–1966)
Resident, Neurology, Cornell University Medical Center (1966–1969)
Major, U.S. Air Force, (1969–1971)
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Institute of Medicine (1992)
National Academy of Sciences (1996)
Fellow, American Association for the Advancement of Science (1996)
Charles A. Dana Award for Pioneering Achievements in Health (1996)
Fellow, American Academy of Arts and Sciences (1998)
Cori Award for Faculty Achievement (inaugural recipient), Washington University (1999)
Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience (1999)
Grawemeyer Award for Psychology (inaugural recipient) (2001)
Goldman-Rakic Award in Cognitive Neuroscience, Brain and Behavior Research Foundation (2004)
University of Washington School of Medicine Distinguished Alumni Award (2006)
Honorary Doctor of Science, University of Chicago (2006)
Ralph W. Gerard Prize in Neuroscience, Society for Neuroscience (2008)
George Miller Prize, Cognitive Neuroscience Society (2009)
MetLife Foundation Award for Medical Research (2011)
Second Century Award, Washington University (2012)

Marcus E. Raichle's research began with studies of human brain circulation and metabolism under the tutelage of Fred Plum and Jerry Posner using the classical techniques developed by Seymour Kety and colleagues. He took that knowledge to Washington University in 1971 where he joined the laboratory of Michel Ter-Pogossian who had initiated the use of cyclotron-produced isotopes in biology and medicine. The announcement of the invention of X-ray computed tomography (CT) in 1973 shifted the focus to imaging and, in the course of the next several years, the first positron emission tomography (PET) scanners were produced in the Ter-Pogossian laboratory. Raichle focused on developing quantitative radiotracer techniques based on cyclotron-produced isotopes to provide the first, quantitative, 3-D images of brain circulation and metabolism in humans with PET. In the 1980s, attention was directed to measuring brain function with PET and, later, with functional magnetic resonance imaging (fMRI). With the help of Michael Posner, functional imaging techniques were combined with detailed analysis of human behaviors. More recently, the emphasis has been on the brain's intrinsic activity as seen with imaging, both fMRI and PET. This work led to the discovery of the brain's default mode network, which plays a central role in the functional organization of the brain in health and disease. Throughout his research, Raichle's work has focused on the origin of imaging signals, neurophysiological as well as metabolic.

Marcus E. Raichle, Sr.

Prologue

I was born on March 15, 1937, in Hoquiam—one of three small towns (Aberdeen, Hoquiam, and Cosmopolis) nestled in the port of Grays Harbor on the coast of Washington State. My parents resided in the neighboring town of Aberdeen where my father, Marcus Simpson Raichle, was a practicing attorney (he later entered the savings and loan business where he worked until retirement). The only hospital in the area was the Hoquiam General Hospital; hence, that is my official birthplace.

My parents were the children of immigrants. My paternal grandfather, John George Raichle, was sent by his parents to the United States at age six with his sister Barbara, age 11, to live with relatives in the Midwest. They were from a family of 13 children residing in Dettingen, Germany, where the Raichle family and its descendants have resided since the 14th century.[1]

The reception of the Raichle children, John and Barbara, was inhospitable, and they were eventually taken in by the Marcus Simpson family of Burlington, Iowa, who raised them; hence my father's given name of Marcus Simpson. My grandfather Raichle married the daughter of another German immigrant family, Sarah Buhrmaster, and moved with his new wife to Yakima, Washington, where he built his own home, which stands to this day. He bought land, started a fruit orchard, and worked as an accountant for one of the large fruit companies in Yakima. The Raichle family of Yakima ultimately consisted of seven children, all of whom attended the University of Washington. My father then attended the University of Washington Law School, graduating at the peak of the Great Depression. He luckily found work upon graduation in a small law firm in Aberdeen, Washington.

My mother's father, Lawrence Hopkinson, emigrated from Leeds, England, where he was a linotype operator.[2] He settled in Milwaukee, Wisconsin, and through his work as a linotype operator was able to raise enough money to bring his bride, Ada Hayward, his father and mother,

[1] For many, the name Raichle is often associated with the famous ski and hiking boots by that name. The business was started by brothers of my grandfather. The Raichle family in Dettingen ran a blacksmith shop behind their home. How boot-making became an interest and a trade is unclear.

[2] My grandfather Lawrence Hopkinson was a descendent of Thomas Hopkinson (1709–51), who immigrated to Philadelphia from England in 1731. He was the first president of the American Philosophical Society and a founder of the University of Pennsylvania. His son, Francis Hopkinson, was a signer of the Declaration of Independence.

brothers and sisters, and eventually some of his wife's relatives to this country. Having accomplished this, he then decided to become a physician. He ultimately graduated from the Milwaukee Medical College and School of Dentistry in the class of 1897. He remained in Milwaukee, where he practiced medicine and continued to participate in the academic affairs of the Milwaukee Medical College. Eventually, he rose to the rank of professor of anatomy and lecturer on rectal diseases. My mother, Dorothy Margaret Hopkinson, was born in Milwaukee, the youngest of four children. She attended Milwaukee Downer College.

Although the Hopkinson family seemed to be thriving in Milwaukee, the climate was a problem for my grandfather (bitterly cold in the winter and hot and humid in the summer) and was in stark contrast to that of England. He ultimately decided to leave Milwaukee and settle in, of all places, Aberdeen, Washington, which at the time was a rough and tumble logging town. Little data exist on the reasons behind this decision other than climate. It is noteworthy, perhaps, that he was a member in good standing of the International Order of Foresters, an organization originating in England but active in North America promoting issues of importance to middle-class families and underserved populations. Likely, in the early 1900s, Aberdeen, Washington, represented an opportunity for someone with these interests.

My parents met and married in Aberdeen where they raised my sister, four years my junior, and me. In those days, Aberdeen, along with its sister communities of Hoquiam and Cosmopolis, was a vibrant place with thriving timber and fishing industries. The local school system, all public except for the local Catholic grade school, was excellent. College attendance rates were high.[3] Extracurricular programs were varied and excellent. I was a mediocre athlete but competed in swimming through graduation.

Among the great strengths of the school system and the community in general were its music programs. Not only were the school programs above average, but this small community even had a respectable symphony orchestra in which I ultimately played. Both of my parents were musical. My mother had a lovely singing voice and, while growing up, regularly accompanied her father, a violinist, on the piano. My father was a gifted piano player who would relax in the evening by sitting down and playing popular music. All he needed was the tune, he could supply the chords! In this environment, I was required to take piano lessons, which I did from kindergarten through high school. In junior high school I fell in love with the oboe, a beautiful instrument when played well, which is something not easily done! I had a masterful teacher, Eugene Stensager, who was part of the high school music

[3] Seven in my high school graduating class of 276 went to Stanford. I was also accepted but opted for the University of Washington, a choice I have never regretted.

program. I had great success as an oboe player in high school[4] and briefly considered a career in music. I have remained an active oboe (and English horn) player to this day as a member of a community symphony orchestra in St. Louis.

The Path to Science

As a reader of this essay, you might be wondering from where the seed of my scientific career came. Although my grandfather was a doctor, I did not enter kindergarten announcing that I wanted to be a physician. I did not own a chemistry set, and I did not collect bugs or other objects of scientific interest. In school, I took all of the science and math courses offered more because it was expected than for any other reason. I did well in these courses but was certainly not the class genius. My parents were told by my high school chemistry teacher, after the first quarter, that I was a daydreamer and needed to be more focused on the class work. (I was receiving a grade of C at the time but managed to pull it up to an A by the end of the year.) I did enjoy my geometry class, particularly working through the "proofs." Solving problems and figuring out how things worked always fascinated me.[5] But the classes in which I did equally well if not better were English, history, and current affairs. These were interests that I shared with my father. We often discussed the political issues of the day. He was a moderate Republican and was very distressed when John Dewey was defeated by that "failed haberdasher" from Missouri. My father would, I suspect, be surprised to know that Harry Truman has become one of my most admired public figures, although given the thoughtful way in which my father approached problems, he too might have become a convert.

My reading (a lifetime habit) during the transition from high school to college was rather wide ranging and foretold, in retrospect, a lifelong array of interests. A few examples may be of interest. The book *Religions of Man* by Houston Smith fueled an interest in the role of religion in society and in my own life, something that I continue to ponder. Winston Churchill's *Triumph and Tragedy*, the final volume in his six-volume series on World War II was a marvelous read, stimulating an interest in history and political

[4] My penultimate performance was the Mozart quartet for oboe, violin, viola, and cello that I performed with my high school classmates Jim Enden and the Cole sisters, winning top honors in the state high music competition. The last time I performed the piece was at our high school graduation.

[5] This dismayed my parents when I was young. They would often find things dismantled, such as the toaster, due to my tinkering and inability to properly reassemble the device. Sometimes it bordered on the serious, I am told, when it involved lamps and light sockets at a time when safety devices to keep the hands of inquisitive children out of danger were not available. The desire to understand how things work has possessed me all of my life and has ranged from the carburetors of my 1960 Mercedes Benz roadster to the brain.

science that endures to this day. And, finally, the marvelous little book by George Gamow, *One, Two, Three Infinity*, was a spell-binding read fueling the latent scientist in me that I was only to discover much later.

Reinforcing my interest in the social sciences and in public affairs was my participation in an American Legion program known as Boys State (there was a separate Girls State in those days!). We spent several weeks on a college campus constructing a state government, which I enjoyed. Emerging from this was my election as a senator from the state of Washington and my subsequent participation in Boys Nation in Washington, D.C., where two from each state came together to operate as a United States Senate. This was a heady experience including sessions in the old Senate chambers of the U.S. Capitol and a meeting with President Eisenhower in the Rose Garden of the White House. After this, I was set to enter the University of Washington in Seattle in the fall of 1955 as a history and political science major with the ultimate goal of law.

I enjoyed college, both the academics and the extracurricular activities. I became a regular member of the University Symphony as an oboe player, president of my fraternity and also rowed with the University of Washington crew. (I was not a great oarsman but I had fun.) By the time I reached my junior year, I was made aware of the fact that I had to take some science courses in order to receive a bachelor's degree from the college of arts and sciences. I had taken some math courses (through calculus) for reasons that escape me after these many years, but these did not qualify. My father suggested that I take zoology as he had when he was at the University of Washington. He even had some of his class notes and drawings, which I deeply regret were subsequently lost or discarded. So, I signed up for the beginning course in zoology, which was the turning point in my career.

In 1959, the introductory course in zoology was taught by a marine biologist named Dixie Lee Ray. She received her PhD from Stanford in marine biology, studying the peripheral nervous system of the fish *Lampanyctus leucopsasus*. The class was attended by several hundred undergraduates, so there was no direct contact with Professor Ray, only with her teaching assistants. Regardless, through her lectures, her effect on the class—and particularly me—was electric. It suddenly made me realize that there was a world of biology out there that had completely escaped my notice.[6] To give you a sense of the impact of Professor Ray on a group of undergraduates, consider the fact that because of her interest in the peaceful use of nuclear energy she was appointed president of the U.S. Atomic Energy Commission by President Richard Nixon in 1973, the only woman ever to serve in this position. She returned to Washington State in 1976 and was elected governor, a post she held until 1981. On learning of her death in 1994, I was

[6] The one science course I had not taken in high school was biology!

saddened by the fact that I had never had the chance to thank her for a career-changing experience, something that I suspect others had undergone as well.

Following my experience in Professor Ray's class, I decided to plunge headfirst into a science curriculum with the aim of going to medical school. Although neither my mother nor my father had ever pressured me in my career decisions, I believe that my mother was quietly pleased when the possibility of my entering medicine emerged. The road ahead was far more challenging for me than I had expected. No class was ever as engaging as the one taught by Professor Ray. But it was not all biology; I essentially had to start over in my junior year taking freshman chemistry and physics. Then, of course, was the dreaded course of organic chemistry, the graveyard for many dreams of attending medical school. At the University of Washington, it was taught by a terrifying figure, Professor Shaw, who had introduced the course to decades of undergraduates by saying, "Look to your right, look to your left, they won't be here by the end of the quarter." I was still there at the end of the quarter but only barely so!

By the time I was approaching the midpoint of my senior year; I had most of the basic requirements for medical school but was still wondering whether I was ready. When I was home for Christmas break, my mother urged me to apply, "What have you got to lose?" (I still have a vivid memory of our conversation.) So, I hastily prepared the application for the University of Washington Medical School and mailed it. Several months passed before I received a letter from the school informing me that I had been rejected. I was disappointed but also eager to know why and what, if anything, it would take to improve my chances for the following year. So, I set up an appointment with the director of admissions.

At my meeting with the medical school director of admissions, I was informed that the reason for my rejection was that I had failed to show up for my interview! I was stunned and even more so when he showed me my application. In my haste to prepare my application I had made an error in my return mailing address (1616 East 47th Street instead of the correct 1617 East 47th street). One incorrect digit and I was faced with a decision: Do I do another year in pre-med or do I return to my original goal of law school? I finally decided that I was going to prove to myself that I could do this. I immediately applied for early admission and scheduled classes for the year that included advanced chemistry and biology. Early in the year, I received an invitation to interview at the University of Washington and shortly thereafter was offered early admission to the class of 1960.

Entering medical school was an exciting experience. A shirt and tie and white coats were required from day one in those more formal times. It was also, for me at least, a somewhat terrifying experience. I was surrounded by classmates most of whom had sought careers in medicine all of their life. Many had parents who were doctors. During our first quarter of classes some

even complained that what we were studying was disappointingly similar to what they had already studied in college. To me everything was frighteningly new. Biochemistry was by far the worst. (I failed my first test!) I was clearly off to a rocky start; but fortunately, things changed in the second half of the first year when we headed into the neuroanatomy/neurophysiology course. This conjoint course was taught by a truly distinguished faculty. At the time, the standard textbook in the field of neurophysiology for medical and graduate students was that edited by Ruch and Patton. They were our professors along with a group of other excellent faculty who seemed to enjoy teaching as much as I enjoyed learning.

A weekly highlight of the neurophysiology/neuroanatomy course was an hour the freshman class spent with the head of neurology, Fred Plum, discussing clinical-pathological correlations. Dr. Plum was the youngest chair of neurology in the country and an articulate but intimidating presence. I will never forget my first exchange with him that occurred during one of these hours. He asked the class what sensory modality was related to itch. I raised my hand, something I rarely did as one of the shyest members of the class, and responded, when he called on me, with "pain." It was the answer he wanted, and he was very complimentary. It was the ego boost of the year!

By the second year of medical school, the playing field had become much more level. The materials were new to all of us making the whole experience for me, in particular, much more enjoyable. It was in my third year of medical school, however, that my career trajectory moved even more in the direction of the neurosciences. Although I enjoyed and did well on my clinical rotations (I loved sewing up wounds, surgical and traumatic; delivering babies; ferreting out the diagnostic significance of heart sounds; as well as talking to patients), my rotation on the neurology service was particularly relevant to my emerging career goals. Once again, Fred Plum played a critical role.

The neurology service was at King County Hospital in downtown Seattle. Each week, Fred Plum would make rounds with the students and house staff on the service. This was a high stress event for all concerned. The two patients to be presented were carefully selected by the chief resident. A separate student was chosen to present each case, and the students were carefully rehearsed by the chief resident prior to rounds with Dr. Plum. The students could not use notes or refer to the patient's chart, which had to be handed to Dr. Plum at the beginning of the presentation. The student stood on the patient's left—across the bed from Dr. Plum. The setting and its preamble were seemingly designed to heighten anxiety in everyone, which they did quite effectively. To add to the drama, on this particular occasion, I was not rehearsed! The reason for this escapes me, but I have the vague recollection it had something to do with a disagreement I had with the chief resident!

The case I presented to Dr. Plum at King County that day in 1963 had symptoms most likely of hysterical origin. I presented the case succinctly and indicated as such. This, my second encounter with Fred Plum, went even better than the first! He seemed especially pleased with my summary of the case. I was clearly on my way to becoming a neurologist.

Later, in my junior year in medical school, Fred Plum was offered the job of chairman of neurology at the New York Hospital–Cornell Medical Center in New York City on the death of his mentor Harold Wolf. I asked him if I could spend my senior elective time with him on the neurology service at the New York Hospital. He agreed. It was a wonderful experience. In addition to my time on the neurology service, I needed to spend some elective time on a surgery rotation. Bronson Ray was then chief of neurosurgery at the New York Hospital. He had been the last resident of Harvey Cushing (the father of American neurosurgery) at the Peter Bent Brigham Hospital in Boston. Although Dr. Ray rarely took students on his service, he agreed to take me for an experience that I treasure to this day. He was a revered man of great dignity in and out of the operating room. There was never any shouting or instrument throwing. I had the distinct honor of holding the sucker on several occasions as he delicately operated on the pituitary gland through a large craniotomy. When I returned to Cornell as a neurology resident, I believe that he was disappointed I did not choose neurosurgery, but a research career was looming ever larger for me and I felt that neurology was a better venue for that (more on that later).

The Medical Scientist Training Program (MSTP) tract that exists in many, if not most, medical schools today, awarding to those lucky enough to be accepted to these programs a joint MD/PhD degree, did not exist when I was in medical school. But the University of Washington, being one of the most academically oriented state medical schools in the country, offered an extra year of training and a master's degree to qualified medical students. I, of course, was not "qualified" as the lone social scientist in our class, and I have to admit that I was very envious of those selected.

During college, with the exception of one summer as a carpenter's apprentice and during the first summers while a medical student, I was a lifeguard for the state of Washington at one of its parks on Puget Sound. It was not until the summer between my junior and senior year that I was able to get a laboratory rotation in the department of orthopedic surgery working with a team of surgeons studying spinal cord development. Although the work in which I was engaged was never published, I loved the experience, which was focused on the microscopic anatomy of the developing rat spinal cord.

A tremendous added plus to that summer's laboratory experience was an early morning class on human neuroanatomy taught by the famous neuropathologist Ellsworth (Buster) Alvord. Each morning at 7 a.m., a small group of us gathered to listen to his lectures on neuroanatomy, and

in parallel, we built models of the human using colored clays and wire. It was the first time that I achieved a clear three-dimensional (3-D) sense of the organization of the human brain. The model I built sits just outside my office to this day.

Graduating from medical school in the spring of 1994, I married my long-time sweetheart, Mary Elizabeth Rupert, also from Aberdeen, who received her undergraduate degree at the same time I received my MD. We had dated on and off for many years and also worked together as lifeguards for the state of Washington. I am writing this in our 50th year together with four grown children (a lawyer, an obstetrician, an economist, and a psychology professor—and 12 grandchildren).

Having spent nine years at the University of Washington, I thought it time to go elsewhere for training. Although I fully intended to become a neurologist and train with Fred Plum at Cornell, his program and many others required a minimum of two years of internal medicine, which I did in Baltimore at Johns Hopkins. In Baltimore, I divided my time between the Baltimore City hospitals and the Johns Hopkins hospital. In those days, a house officer's schedule was 24/7 and all night every other day and every other weekend. It was stimulating and exhausting. But somehow the research bug had taken hold, and I found myself pursuing a number of things in the context of my clinical work.

An example of the type of research I did as a medical intern and resident was the analysis of spinal fluid in patients with intracranial bleeding. At the time, the breakdown of hemoglobin in spinal fluid, its chemistry and temporal dynamics, was reasonably well characterized but using it to estimate the onset of bleeding in individual patients had not been actively pursued. The instrumentation necessary to characterize the breakdown products of hemoglobin in cerebrospinal fluid existed in the laboratory of the National Institute of Aging situated on the campus of the Baltimore City hospitals. The laboratory was under the direction of Rubin Andrus. He was most agreeable to my coming to his laboratory at any hour of the day or night to analyze my specimens on his instruments. I had great fun doing this work through two years in the Hopkins system, and although I never published my results, which would have been difficult under the circumstances, I derived great satisfaction in collecting and analyzing data. I even organized a "research day" with other house officers where we presented our work to the attending medical staff that included Julius Krevans, who later became dean of medicine at the University of California, San Francisco, and Charley Carpenter, a world expert on cholera who subsequently became head of medicine at Case-Western Reserve School of Medicine.

In the summer of 1966, we moved to New York City to begin my neurology residency. Clinical duties dominated my time particularly in the first year of my residency. However, Plum made it clear that we were in a program that not only expected excellence in the clinic but also an acknowledgment

of the importance of research. Emphasis was placed on how we thought about a problem, not whether we had the answer. At the time, Plum and his long-time collaborator Jerry Posner were pioneering a new, systematic approach to the problems of stupor and coma that placed special emphasis on the recognition and remediation of reversible causes, largely metabolic. As residents, we were learning a new approach to these problems with the galley proofs of the first edition of their classic monograph *Stupor and Coma*.

My first serious foray into research as a resident again began during my second year when I was the consult resident for the New York Hospital. This was a maturing experience where you operated largely on your own as a consultant to all of the services of the hospital. Of course, you had a backup, usually Plum, but you were expected to take charge. A year or two before I began this rotation, investigators at the Massachusetts General Hospital had introduced the use of massive doses of intravenous penicillin as a treatment for deadly, gram-negative bacterial infections. Although the therapy was effective in treating the infection, it had unexpected and unintended side effects. These manifest as the sudden onset of confusion and random jerking movements of the large muscle groups of the body (i.e., so-called multifocal myoclonus) that were aggravated by any attempt on the part of the patient to move. In some patients, the syndrome progressed to frank seizures and coma. All of this was typical of a metabolic encephalopathy. I realized that I was seeing increasing numbers of these patients. Although they presented with a variety of medical problems, the common denominator was the fact that they were all on high doses of penicillin.

From a neuroscience perspective, it had been known for some time that penicillin was epileptogenic when applied directly to the cortex of experimental animals. The idea that it could behave in a similar fashion when given systemically in large doses was less well appreciated and, prior to the use of massive does, was probably never encountered. When it was encountered, the clinical situation was often complicated with other conditions such as kidney failure, which could also cause a similar encephalopathy.

Clearly, there needed to be a carefully controlled study of the problem in the laboratory. To explore this association in more detail, I sought the assistance of Sidney Lewis, Henn Kutt, and Fletcher McDowell, members of the neurology faculty at Cornell with a research interest in epilepsy and with a laboratory fully equipped for small animal research of the type needed for this type of study. Working nights and weekends in the Lewis/Kutt/McDowell laboratory, I was able to sort this out with studies in 13 cats and 36 rats. Our most noteworthy finding was that intravenously administered penicillin produced an encephalopathy in animals that was similar in all respects to that observed in humans except that the effective dose was species specific—with cats most susceptible and humans least. Also, the toxic effect of penicillin on the brain was directly related to its antibacterial activity. This study led to my first published scientific paper, which appeared

in the *Archives of Neurology* in 1971 (Raichle, Kutt, Louis, and McDowell, 1971). I had finally gone from bedside to bench, casting light on an important clinical problem and learning in the process how to do well-controlled experiments, analyze data, and write a publishable manuscript (probably the most challenging part of all). But doing this on nights and weekends was not ideal for preparing me in the ways of scientific research such that I could eventually operate on my own. Thus, I sought time off from my residency to work full time in the laboratory with Fred Plum and Jerry Posner.

As mentioned earlier, Fred and Jerry were deeply committed to an understanding of the metabolic causes of coma, and in the course of their research, quantitative measurements of brain blood flow and metabolism became increasingly important to their objectives. Fortunately, Seymour Kety and Carl Schmidt of the University of Pennsylvania had laid the groundwork for these measurements in the late 1940s (Kety and Schmidt, 1948). The majority of the work of Kety, Schmidt, and their colleagues focused on making measurements in humans. As a result, they were the first to provide us with quantitative measurements of human whole brain blood flow and oxygen consumption. To this day, their technique remains the "gold standard" of such measurements.

It is worth noting what was involved in the Kety/Schmidt technique as applied to humans. The technique was based on the Fick principle that, in essence, says that by measuring the blood concentration of what is presented to an organ minus what is leaving, combined with the rate of blood flowing to the organ, one can compute the rate at which, in their case, oxygen was used.[7] The trick was how to measure, quantitatively, the blood flow. They devised an ingenious technique using the inert diffusible gas nitrous oxide and measuring the concentrations of the gas in arterial and in venous blood across the brain. This they did by placing a catheter in the femoral artery in the groin and a second catheter in the jugular bulb. From these data, it was possible to compute the blood flow to the brain. In the Plum and Posner implementation of the Kety-Schmidt technique, the radioactive inert gas Krypton 85 was substituted for nitrous oxide, making measurements of its concentration history in arterial and venous blood much easier.

The experimental question I inherited on entry into the Plum-Posner lab was determining whether the hydrogen ion was important in the matching of brain circulation to its metabolic needs. The logic behind the question emerged from two observations. First, the normal fuel for brain energy metabolism is glucose, and the metabolic extraction of its potential energy produces carbon dioxide and water. Thus, as glucose is consumed, carbon dioxide increases. Second, acute changes in arterial blood and, concomitantly,

[7] This, of course, can be applied to other metabolites, most noteworthy being glucose as well as lactate, an important product of glucose metabolism.

brain carbon dioxide tension have immediate and profound effects on brain blood flow (i.e., increases in carbon dioxide tension by inhaling low concentrations of carbon dioxide cause increases in blood flow, and hyperventilation causes a decrease). The answer seemed obvious—carbon dioxide was acting on brain blood vessels to change blood flow. Unfortunately, the situation was a bit more complicated. Changing the amount of dissolved carbon dioxide in the brain has a direct effect on brain pH because the brain is buffered by bicarbonate.[8]

The key to separating the roles of carbon dioxide and pH is the fact that the brain appears to normalize its pH during sustained periods of hyperventilation,[9] suggesting to us that, if we hyperventilated anesthetized laboratory animals for several hours, we would see an initial drop in blood flow that returned to control levels despite significantly reduced arterial carbon dioxide tensions. However, despite carefully controlled ventilation and levels of anesthesia, we failed to observe the predicted change. In fact, blood flow not only dropped initially with the onset of hyperventilation but continued to fall during the five hours of the experiment. In a control experiment with arterial carbon dioxide tension maintained at a normal level, blood flow again fell across the five hours of observation. We could not explain this declining blood flow other than to surmise that it represented an unstable experimental preparation. The alternative we arrived at was to use ourselves as the experimental subjects. After all, the high altitude experiments leading to our work were done in humans, and the techniques we were using to measure brain blood flow and metabolism had been validated in humans by Kety, Schmidt, and their colleagues.

Not knowing for sure just how this was going to play out, I volunteered to go first. Gordon Potts, newly head of neuroradiology at the New York Hospital and later to become one of the leading neuroradiologists in the world, placed the catheters in my jugular bulb[10] and femoral artery while I lay in a hospital bed in the same laboratory in which we had conducted our animal experiments.[11] I was fitted with a face mask for the inhalation of the radioactive gas to measure blood flow and also for the monitoring of my end-tidal CO_2. An end-tidal CO_2 meter was placed in front of me so that

[8] The basic relationship of carbon dioxide to bicarbonate was first described by Lawrence Henderson in 1908 and later expressed by Karl Hasselbalch in logarithmic form. Crediting the work of both, it is classically referred to as the Henderson-Hasselbalch equation. Carbon dioxide concentration is the numerator and bicarbonate is the denominator of this simple equation. Decreasing carbon dioxide concentration decreases hydrogen ion concentration (i.e., increases pH, which is the negative logarithm of the hydrogen ion concentration).

[9] This was observed in high altitude experiments performed by John Severinghaus, Tom Hornbein, and their colleagues.

[10] I will never forget the squeaking sound in my right ear as the catheter was advanced percutaneously into my jugular bulb.

[11] No consent form was signed and no consultation with an institutional human studies review board even discussed!

I could monitor my respirations. My brain blood flow and metabolism were measured at the beginning of the experiment while I relaxed, breathing at a normal rate.

Then the ordeal began—hyperventilating sufficiently vigorously to reduce my arterial carbon dioxide tension to half its normal value and holding it there by continuing to hyperventilate for five hours. Fred and Jerry took turns cheering me on while repeatedly measuring my brain blood flow and metabolism. Once in the routine, it was somewhat less difficult than I had imagined. At the end of five hours, I had to suddenly stop my hyperventilation, forcing my arterial carbon dioxide tension back to control. This proved to be rather difficult. Jerry Posner was next and somewhat more accustomed to the experience, having done the protocol once before without measurements of blood flow. Finally, it was Fred's turn. He soldiered through without a problem until the very end when he suddenly had a shaking chill. Although never verified, we suspected sepsis—even though an autonomic reaction to the ordeal, in retrospect, was equally likely. For Jerry and me, the relief in getting through this was enormous (something like boot camp in the world of cerebral blood flow and metabolism). The relief was short-lived. The morning following Fred's experiment he announced that we all needed to do it again to boost the "n"! Fortunately, the vote was two to one against, and Fred clearly had no alternative subjects waiting in the wings.

The data arising from this study proved to be exceptional (three measurements of blood flow, oxygen consumption, glucose utilization and lactate production before, during, and after sustained hyperventilation plus an additional subject, Jerry Posner, with arteriovenous difference measurements of all of the metabolites). The results definitely supported the hypothesis that the effect of carbon dioxide on blood flow was mediated by the hydrogen ion. In addition, the study's comprehensive, quantitative data has proven invaluable to the present day.

Following my time in the laboratory with Fred and Jerry, I returned to my residency training, finishing in the spring of 1969 at the peak of the Vietnam War. Military service was a given for all MDs not heading to the National Institutes of Health (NIH). My service had been deferred until the completion of my residency at which time I was commissioned a major in the U.S. Air Force and assigned to the School of Aerospace Medicine. The experience there proved to be another important stepping-stone to my academic career.

The School of Aerospace Medicine had several missions. I was formally assigned to the medical evaluation unit staffed by a range of specialists, including four neurologists. Some of the physicians were career military officers, others like me were in for two years, and there were a few civilians. I was very impressed by the caliber of these individuals and by their dedication. Our job was to evaluate flying personnel in the Air Force (largely pilots and navigators) who had experienced a medical problem potentially impairing their ability to fly. We also did the medical screening of the Air

Force Research Pilots (the people who would go out to Edwards Air Force Base and fly exotic new aircraft) and of the pilots who flew the U2 and SR71 planes.

In order to understand the conditions faced by the individuals we were expected to evaluate, we were strongly encouraged to attend the Air Force Flight Surgeons School as well as to attain qualifications in hyperbaric medicine (i.e., chamber certification in diving and altitude chambers). After all of this, we were placed on flying status and expected to fly on a regular basis. Given that the school did not have its own flying wing, we could pick and choose among the many aircraft at other bases. I did so liberally and enjoyed every minute of it.

Although my medical experience at the School of Aerospace Medicine was remarkable in many ways, putting the whole matter of brain function into an entirely new context, I was also exposed to a most remarkable research experience. In addition to its medical role, at that time, the School of Aerospace Medicine was very involved in understanding human adaptation to space flight. This was in part related to the intention of the air force to place a spy satellite in space and also related to the early work of NASA.[12] In pursuit of this, the military had assembled a remarkably talented group of civilian PhDs in the area of cardiovascular and pulmonary physiology and equipped them with absolutely remarkable research laboratories for the time. Although some human research was being conducted, the primary work was performed on rhesus monkeys. The school had a colony of 1,500 monkeys attended by a core of veterinarians.

Somehow the word got out that I had done research on brain circulation and metabolism with Fred Plum and Jerry Posner, and I was recruited to work with Lowell Stone, a young PhD in cardiovascular physiology who some years later became chair of physiology at the University of Oklahoma. His technique was to chronically implant Doppler flow probes on arteries of interest and monitor changes in blood flow continuously under a variety of experimental conditions. What they proposed was that they would teach me the techniques of implanting the probes and measuring flow if I would work with them on studies of brain circulation. The veterinarians were superb surgeons, and I quickly learned how to isolate the internal carotid artery and implant the probes. We even went so far as to implant a few probes on the middle cerebral artery. In addition, we developed in implantable device in the skull of the monkey over the superior sagittal sinus that allowed chronic sampling of cerebral venous blood. I was "handed the keys" to a Grass polygraph and told to learn how to use it. Our data were recorded on FM tape and analyzed on a massive analogue computer at the school that

[12] All of the original Mercury astronauts were medically evaluated at the School of Aerospace Medicine.

ran on vacuum tubes and was programmed uniquely for each study using a large "circuit" board and wires. It was an exciting time and yet relaxed when compared to the rather high intensity neurology residency I had experienced under Fred Plum.

To my surprise, one day at the school I received a letter from the organizing committee of a meeting on brain blood flow and metabolism to be held at the Royal College of Physicians in London. Unbeknownst to me, Fred Plum had submitted an abstract of our hyperventilation experiment and, as I later learned, he expected to be asked to present our data. The organizing committee, apparently seeing my name first, sent me the acceptance letter. I was delighted and immediately began figuring out how I was going to get to London—my first trip to Europe. My commanding officer kindly agreed to give me the time off to attend the meeting.

It is customary in the air force to look for planes going your way and to ask to tag along. The best jumping off place at the time was Dover Air Force Base in Delaware, so I got on an air force plane from San Antonio to Dover and went in to base operations to see what my options were. As it turned out, the only option available was to join an Iranian air crew that was flying a brand new C141 transport plane to Tehran via London. In my flight suit sporting my flight surgeon wings, I approached the crew, and they invited me along. The only problem was, initially, they did not understand the difference between a flight surgeon and a pilot (anyone in a flight suit sporting wings must be a pilot!). They kept insisting that I take the left seat and fly the plane. Fortunately, we managed to get to London safely.

Of course, I enjoyed my first presentation at an international meeting to a group of individuals who were already legends in the field of cerebral blood flow and metabolism. Many would become close friends over subsequent years. This meeting, however, was unexpectedly important in another way. Presenting one of the most interesting papers in London in 1970 was a PhD physicist from Washington University in St Louis by the name of Michel Ter-Pogossian.

Michel Ter-Pogossian was born in Berlin and grew up in Paris. His father was a member of the French diplomatic service prior to World War II. During the war, Michel allegedly worked for the French underground. Following the war, he came to the United States and Washington University to study physics. One of the motivating factors in his decision to choose Washington University was the fact that the chancellor was Arthur Holley Compton, a Nobel laureate in physics. The other factor was that Washington University had a cyclotron that, in its day, was a fairly substantial machine.

The cyclotron was purchased at the behest of the Mallinckrodt Institute of Radiology at Washington University (i.e., the department of radiology) to produce isotopes for nuclear medicine. Shortly after the cyclotron was commissioned, the United States entered World War II and the cyclotron became a major component of the Manhattan Project. When the war was

over, cyclotron-produced isotopes were no longer of interest to nuclear medicine because of the more conveniently available generator-produced isotopes. Therefore, the cyclotron became a tool for research in chemistry and physics.

Into the setting of a now-available cyclotron on the Washington University campus and a team of chemists versed in its use from their experience in the Manhattan Project, came Michel Ter-Pogossian, an eager young graduate student. In the course of his graduate work, he became interested in the potential of cyclotron-produced isotopes for research in biology and medicine,[13] a theme that he was to pursue throughout his entire academic career at Washington University. The isotope of particular interest to Ter-Pogossian at the time was ^{15}O (half-life two minutes). To pursue his interest and convince others of its importance, he set up a small laboratory in a house trailer just outside of the cyclotron building. Into the building, he rigged a connection directly to the beam line of the cyclotron, permitting the administration of ^{15}O-labeled air to rodents (they simply breathed the labeled air as it came into a small container in which they were placed). He then imaged the animals immediately after the brief exposure, using a simple nuclear medicine camera of the day. The resulting "images"[14] were sufficiently impressive that the Mallinckrodt Institute of Radiology (MIR) agreed to put a small medical cyclotron in the basement of the institute.

Once the cyclotron was up and running in the MIR, the brain became a significant focus of attention. One of the compelling reasons for the emphasis on the brain was the fact that it was a large organ nicely isolated from other organs and, in contrast to the heart, it did not move. Also, friendships mattered. The then-head of the MIR was Juan Taveras, arguably the father of American neuroradiology and whose research interests centered around measurements of brain blood flow. Without his support, the cyclotron would never have been installed in the MIR. Also, Sam Guze, head of psychiatry and vice chancellor for medical affairs and a close friend of Ter-Pogossian's, was very interested in the possibility of using measures of brain metabolism to study patients with psychiatric disease.

Two additional factors propelled brain studies with cyclotron-produced isotopes forward. First, Michael Welch, a young radiochemist who received his PhD at University College London and a postdoc at the Brookhaven National Laboratory, joined the Ter-Pogossian laboratory and immediately made the synthesis of ^{15}O-labeled water, oxygen, and carbon monoxide routine. ^{15}O-labeled water was selected as the inert, diffusible tracer for the measurement of brain blood flow. ^{15}O-carbon monoxide was the tracer for

[13] This was in part stimulated by the work ongoing at the Hammersmith Hospital in London where the first cyclotron for biomedical research had been installed in a hospital setting several years earlier.

[14] These experiments were occurring more than two decades before the introduction of imaging as we know it today.

the measurement of brain blood volume because of its irreversible binding to hemoglobin. And, ^{15}O-labeled oxygen was, in combination with the other two tracers, the key to measuring brain oxygen consumption. Second, a radiation detector system was constructed that was capable of assessing the concentration of these ^{15}O-labeled radiopharmaceuticals in the human brain. The detectors, three on each side of the head, had to be shielded in substantial quantities of lead in order to capture the regional distribution of these high energy isotopes.[15]

With appropriate radiopharmaceuticals in hand and a detector system suitable for detecting them in the brain, research began to determine whether regional oxygen consumption could be measured in the human brain. It was the result of these very earliest experiments (Ter-Pogossian, Eichling, Davis, and Welch, 1970) that Michel Ter-Pogossian presented at the meeting in London in 1970 that I attended. At the meeting, he approached me and asked if I would be interested in joining his group in St. Louis to pursue studies of brain circulation and metabolism with cyclotron-produced radiopharmaceuticals. The prospect of being able to measure brain oxygen consumption regionally in humans for the first time was an opportunity too attractive to pass up.

I joined the faculty of Washington University School of Medicine in the summer of 1971 and have been a member of the faculty ever since. In retrospect, the appointment was unique in several ways. I was a clinically trained neurologist with a background in measurements of brain circulation and metabolism, recruited by a physicist (Michel Ter-Pogossian) to work in a radiology department laboratory populated by physicists, chemists, engineers, applied mathematicians, and computer scientists along with talented cyclotron operators, machinists, and technicians. At the time I was the only neuroscientist in the lab. Such an environment today would be considered typical of an interdisciplinary research operation, but, at the time, no one spoke of us in those terms.

The other important feature of the Ter-Pogossian lab was the fact that most of us resided in rather cramped quarters on the sixth floor of the MIR with the cyclotron in the basement, the neuroradiology suite with some of our research equipment on the third floor, and animal quarters, labs, and surgery on the floors above us. Interactions were inescapable and incredibly valuable.

Initially, I had a joint appointment in radiology and neurology, which has expanded over the years to include neurobiology, psychology, and biomedi-

[15] Positron-emitting radionuclides decay by the emission of a positron that travels a few millimeters in tissue before interacting with an electron. This interaction produces a pair of 511 keV photons traveling at 180^0 from each other. Prior to the invention of positron emission tomography (PET), the only way to know where this radiation was coming from was to surround detectors with lead to focus or collimate what they received.

cal engineering. My laboratory has always resided in the MIR. Initially, I was a member of the Ter-Pogossian laboratory but eventually acquired my own laboratory known as the Neuroimaging Laboratory, which presently consists of 23 faculty members from five departments in the university (radiology, neurology, psychiatry, psychology, and pediatrics) and 100 staff, students, and postdocs.

My introduction to the use of the ^{15}O-labeled radiopharmaceuticals involved experiments in monkeys and humans. At the time, these radiopharmaceuticals were administered directly into the internal carotid artery by way of a catheter introduced into the femoral artery and threaded there under fluoroscopic control, a technique I mastered with the help of the MIR neuroradiologists. All human studies were performed on patients undergoing carotid angiography as part of the clinical evaluation. Data were collected on a classic Laboratory Instrument Computer (LINC) but analyzed by hand because of the limited computational capability of the LINC.[16] Our initial objective was to validate the Ter-Pogossian method for the measurement of regional brain oxygen consumption, a technique he developed with his graduate student John Eichling. Having been schooled in the gold standard for such measurements in the Plum/Posner laboratory, it was a straightforward problem. The technique came through with flying colors (Raichle, Grubb, Eichling, and Ter-Pogossian, 1976).

In the early experiments in the Ter-Pogossian lab we discovered that ^{15}O-labeled water was not, as advertised, a freely diffusible tracer. Although this was not an impediment in our use of the tracer for the measurement of blood flow, it opened up a line of investigation that remains incomplete to this day. The tantalizing insight that this discovery provided was the fact that the blood brain barrier was a flexible membrane that, with respect to water, mirrored many of the features and functions of the distal tubule of the kidney. We were having great fun pursuing this and other novel and unexpected findings when an event occurred that not only changed the practice of medicine but also opened up the prospect of safely obtaining true 3-D images of the anatomy and the function of the human brain. It was the invention of X-ray computed tomography by Godfrey Hounsfield, a self-taught engineering genius working for EMI Limited in England.

The Invention of Positron Emission Tomography

When first introduced, X-ray computed tomography (CT) only created images of the brain.[17] The initial reaction to CT by the computer science

[16] Data consisted of residue curves following a pulse injection of the radiopharmaceutical into the internal carotid artery. The data were printed out on semilog paper for analysis. Several analysis strategies were employed as described in our early papers.

[17] It is of historical interest that the original CT scanner, known at the time as the EMI scanner

and engineering folks in the lab was that they could design a better CT. It was certainly the case that the machine designed and built by Hounsfield achieved its success through a brute force engineering approach. Engineering niceties had been sacrificed in the interest of getting the job done. Work began almost immediately to create a new reconstruction algorithm, and collaboration was established between the MIR and a leading manufacturer of radiology equipment.

Meanwhile EMI began marketing their new scanners, and several major hospitals were acquiring them including the National Hospital for Neurological Diseases in Queens Square, London; the Massachusetts General Hospital; and the Mayo Clinic. This was too much for the then director of MIR, Ron Evens. He wanted MIR to be among the first to have this new device and waiting on algorithmic developments at Washington University and manufacturing elsewhere became unacceptable. He canceled the outside contract and immediately purchased an EMI scanner for the MIR. It was, as I recall, the fourth installed worldwide.

The cancellation of a project to build our own CT scanner was initially greeted with great disappointment, particularly by Jerry Cox and Don Snyder, the two engineers who had developed a CT algorithm that was ultimately to become one of the standards of the field. However, a casual afternoon conversation in the office next to mine on the sixth floor of MIR changed that. The conversation took place between Jerry Cox, whose orphaned algorithm was in need of a project, and Michel Phelps, a nuclear chemist who had joined the Ter-Pogossian laboratory at the same time I did. In the course of their conversation, Phelps asked Cox whether it might be possible to use his algorithm to reconstruct in 3-D the distribution of compounds labeled with positron-emitting radionuclides such as ^{15}O, ^{11}C, ^{13}N, and ^{18}F.

An important element of the conversation between Cox and Phelps concerned the decay scheme of these radionuclides, which consisted of two high-energy photons going in opposite directions (i.e., precisely 180 degrees from each other) when a positron interacts with an electron in the tissue. In its simplest form, imagine placing two radiation detectors facing each other with the brain in between. When an event (i.e., a photon) is detected simultaneously by both detectors, the inference to be drawn is that an event has occurred on a line between the two detectors. Placing two detectors together in this manner is known as a coincidence circuit or detector. After going to the blackboard and doing the math the answer from Jerry was "yes."

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for the company in which it was developed, was specifically designed to image the brain. The reason for this had largely to do with the sources of funding available to Hounsfield and his colleagues (for historical reviews see Raichle, 2000).

Phelps immediately seized upon the idea and brought it up with Ter-Pogossian who was not enthusiastic. Undaunted, Phelps and a young postdoc in the lab by the name of Ed Hoffman along with some electronics, a couple of detectors, and some lead blocks and, of course, Jerry and Don's algorithm, worked nights and weekends to show that the idea was not only theoretically sound but feasible given the current state of electronics and computers. More proof was needed, however, to convince Ter-Pogossian. I was approached because I had the requisite number of detectors and electronics needed for the feasibility study. These were the components of a 26-probe detector system that had been built in the lab for me to conduct experiments on patients undergoing cerebral angiography for diagnostic purposes. It was situated in the third-floor angiogram suite of the MIR along with connections to our computers on the sixth floor and a pneumatic line to the cyclotron in the basement for the transmission of ^{15}O-labeled water, oxygen, and carbon monoxide. Although I do not recall the conversations, I was obviously persuaded to relinquish the use of my detector system, which was never rebuilt, for the purpose of proving that the concept of positron emission tomography (PET) was viable. The resulting evidence obtained was sufficient to convince even Ter-Pogossian that the idea had merit. He brought the full resources of the lab to bear on the matter and, in short order, the first human PET scanner was conceived and built. It was called PETT III for positron emission transaxial tomograph and "III" because it followed the two initial tabletop versions. The first human study was performed in April 1974 and the full description of the scanner appeared in two papers published in 1975 (Phelps, Hoffman, Mullani, and Ter-Pogossian, 1975; Ter-Pogossian, Phelps, Hoffman, and Mullani, 1975).

Brain Mapping with Positron Emission Tomography

Obviously, I was a bystander in the actual building of the first PET scanner, but I had a ringside seat. It was clear that, if we were to exploit the ability of this instrument to make truly quantitative 3-D images of blood flow and metabolism in the human brain, there was still much work to be done. An initial element of the effort focused on our understanding of ^{15}O-labeled water as a blood flow tracer. The idea was to use it as Seymour Kety and colleagues had used trifluoroiodomethane as a blood flow tracer for the measurement of blood flow autoradiographically in laboratory animals. In animals, the tracer was administered intravenously and a minute later the animal was sacrificed, the brain removed, frozen, carefully sliced, and laid on X-ray film. From the arterial time-activity curve of the tracer and the quantitative autoradiogram, they were able to calculate blood flow. Our idea was to substitute a quantitative PET image for the autoradiogram and make the same calculation. It actually worked splendidly until we decided to extend the duration of the PET scan beyond one minute and discovered

that the longer the scan the lower the computed flow. After much theorizing and experimentation, we concluded that the simple one-compartment model used by Kety and associates only worked when all or most of the tracer remained within the brain during the experiment (one minute was the limit!) (Landau, Freygang, Roland, Sokoloff, and Kety, 1955; Kety, 1960). Some years later, I asked Seymour why they chose a minute, and he told me that when they went longer the values decreased, something not mentioned in any of their papers!

Implementing a means of measuring oxygen consumption proved more difficult. When a small amount of a patient's or an animal's blood labeled $O^{15}O$ was injected into the carotid artery, it was relatively easy to quantitatively estimate the fraction of available oxygen extracted by the brain. Knowing this plus the arterial oxygen content and the blood flow, the calculation of oxygen consumption was straightforward and accurate. In PET, the $O^{15}O$ was inhaled. Some of it was taken up by the brain and converted to water, which left the brain like a blood flow tracer. Some of the administered oxygen remained in blood as oxyhemoglobin behaving like a blood volume tracer. The difference with regard to the brain represented the fraction extracted, but this could not be estimated from the $O^{15}O$ data alone. Therefore, the inhalation of $O^{15}O$ was followed by an inhalation of $C^{15}O$ to measure blood volume (as required by the model) and an intravenous administration of $H_2{}^{15}O$ to measure blood flow. (We now refer to this cocktail of radiopharmaceuticals as a "triple pack.") With Peter Herscovitch and Mark Mintun taking the lead, we developed and validated a model incorporating the data from these three tracer administrations to calculate regional oxygen consumption with PET (Mintun, Raichle, Martin, and Herscovitch, 1984). Knowing that we had a truly validated means of measuring brain oxygen consumption regionally proved to be invaluable as our work unfolded.

By 1980, an interest emerged in the lab in using PET to map functional activity in the brain. Work of this type had already begun using a PET adaptation of Lou Sokoloff's ^{14}C-deoxyglucose autoradiographic technique for the measurement of regional brain glucose utilization.[18] The PET adaptation used ^{18}F-deoxyglucose or FDG as it is most commonly known (Phelps et al., 1979; Reivich et al., 1979). As Sokoloff had shown in animals, the PET-FDG technique demonstrated a wide variety of task-specific changes in regional glucose metabolism in normal human subjects. From a brain mapping perspective, however, this technique had one critical limitation, the time necessary to make a single measurement, which was 40 minutes. The time was required to allow non-metabolized tracer to clear from the tissue.

[18] Deoxyglucose is an analogue of glucose and is readily taken up by brain cells and phosphorylated to deoxyglucose-6-phosphate. In contrast to glucose, deoxyglucose cannot be metabolized further and cannot be dephosphorylated. As a result, it is trapped in the cell in an amount that reflects the rate of the initial step in glucose metabolism.

For steady state measurements of baseline metabolism, this was satisfactory, but for complex behavioral paradigms, this was a serious problem. The additional problem with FDG was its half-life of 110 minutes, which meant that considerable time (usually five half- lives) was needed between measurements for activity within the body to decay. For us the answer was blood flow.

Using measures of blood flow to map responses to changes in activity dates back to the late 1800s when Angelo Mosso first introduced the idea (Mosso, 1881). Kety, Sokoloff, and their colleagues introduced the technique in more quantitative terms with the autoradiographic technique (Kety, 1960). The idea was subsequently introduced in humans in the 1960s by David Ingvar, Jarl Risberg, Niels Lassen, and their Scandinavian colleagues (Lassen, Ingvar, and Skinhoj, 1978). They used ^{133} Xenon. In their first experiments, the tracer was injected directly into the carotid artery. Later, Xenon was administered by inhalation. They monitored regional blood with radiation detectors arranged about the head in a helmet-like fashion. At the peak of their work, they were measuring activity in approximately 256 cortical regions. Although this was not a true 3-D representation of blood flow in the brain, it did give a good sense that regional changes did occur during task performance. Their measurement took approximately two minutes and could be repeated at least one time.

Blood flow measured with $H_2{}^{15}O$ as we had developed it for PET could be measured in less than a minute, repeated every 10 minutes due to the short half-life of ^{15}O (two minutes), and repeated up to 12 times in a single experiment because of the low radiation dose, also a feature of the very short half-life. Because the use of ^{15}O-labeled tracers had been a staple of the laboratory even before I arrived, producing and handling $H_2{}^{15}O$ with its short half-life (a two-minute half- life means all radioactivity has decayed in 10 minutes or five half-lives) had become a routine.

Because of our desire to take full advantage of the capabilities of ^{15}O-labeled water as well as oxygen and carbon monoxide, we had designed and built in our laboratory a PET scanner optimized for this purpose. This was PET VI, an instrument meant specifically for brain research with full brain coverage and high count rate capability (Ter-Pogossian, Ficke, Hood, Yamamoto, and Mullani, 1982). It was, in my estimation, the best PET scanner ever built at Washington University. It served us superbly for 13 years (1980–1993) during which time all of the basic tools of brain mapping in cognitive neuroscience were developed and introduced.

Once equipped with a means of measuring blood flow repeatedly in a single experiment the next problem was to know the exact location of the changes we observed. Although various approaches had been proposed by others (for a more detailed review see Raichle, 2000), we were particularly attracted to the work of Professor Talairach (Talairach, Szikla,

and Tournoux, 1967), a well-known French neuroradiologist. His beautifully developed stereotaxic means of localization in the human brain was designed for neurosurgeons and based on skull landmarks (i.e., the anterior-posterior commissural line). Working from his 1967 atlas, which was only available in France, we were able to implement his strategy by obtaining a lateral skull X-ray in all of our subjects while in the PET scanner. The orientation of the PET slices was imprinted on the X-ray using a small grid placed beside the subject's head while obtaining the X-ray. With this information, we were able to relate the data from each subject to the HD6 brain in the Talairach atlas (Fox, Perlmutter, and Raichle, 1985). This was definitely a major step forward for us, but we had additional hurdles to overcome.

Data from individual subjects were often noisy. This raised the question of averaging across subjects to increase signal and reduce noise. This became a hotly debated subject in the lab. Proponents of averaging were certain that it would improve our data, but opponents argued that individual differences were simply too great even after careful stereotaxic registration to a common atlas space. The person most insistent that we try averaging was Eric Reiman, a young psychiatrist working in the lab. Mark Mintun, another young member of the lab and a physician trained in nuclear medicine and an MIT graduate with the mathematical and computer skills necessary to implement averaging, agreed to tackle the problem if Eric could raise the money to hire a programmer to assist. Approached by Eric, Sam Guze, head of psychiatry, agreed to provide the funds, and the work began. It took Mark close to a year to implement a strategy that was initially tried on a group of individuals undergoing a somatosensory stimulation paradigm. I do not believe that anyone present in the lab the day the first results of this effort were unveiled will ever forget the experience. The signal was enhanced and the noise suppressed in a most spectacular fashion (Fox, Mintun, Reiman, and Raichle, 1988). Also immediately suppressed were any doubts that averaging would work!

The next hurdle was deciding what was significant in our images. It was easy enough when the experiment was one of hypothesis testing. For example, does primary somatosensory cortex increase its activity when we stimulate the contralateral hand? We now had a means of anatomically localizing somatosensory cortex in a common anatomical space. Because we could make multiple measurements in each subject, we could measure the activity level before and after stimulation. With these paired measurements confined to a specific location in the brain, the statistics were straightforward. However, we were interested in much more complex stimuli and behaviors where results could not be predicted in advance. It was obvious even before we ventured there that we needed to develop a statistical strategy that allowed us to conduct *hypothesis-generating* experiments with

reasonable efficiency.[19] After all, we were venturing into unknown territory where it would have been presumptuous to assume that we knew in advance how the human brain was organized. We finally agreed on a statistical approach that, while incomplete, allowed us to move forward with our work (Fox, Mintun, Reiman, and Raichle, 1988). Much work on this problem has taken place since in laboratories worldwide resulting in strategies that are quite satisfactory.

The final piece of the puzzle was how to design the behavioral aspects of our studies that respected the constraints of the imaging environment but also dealt in a principled way with the complexities of human behavior. One of St. Louis's most generous philanthropists, James S. McDonnell, came to the rescue. In addition to founding the McDonnell-Douglas aircraft company, he had a lifelong interest in the brain. Shortly before his death, he approached Washington University with a proposal to fund a brain research center focusing on the relationship between human behaviors and brain function. A proposal was drafted that, as Mr. McDonnell requested, included the hiring of a psychologist to direct the behavioral aspects of the research. Fortunately for everyone concerned, the person recruited was Michael Posner from the University of Oregon, one of the world's leading cognitive psychologists.

Cognitive psychologists had pioneered behavioral strategies designed to dissect human behaviors into their component operations by combining tasks containing the operation of interest with sophisticated control conditions that contained all but the operation of interest (for example see Posner, 1986). A moment's reflection should reveal just how perfectly this strategy meshed with the imaging strategies we had been developing. Mike fit into the imaging operation at Washington University like an eager young postdoc. We tackled many exciting things while he was with us (he returned to Oregon at the end of the 1980s) but probably the most enduring was our study of the cortical processing of single words.

Understanding the organization of language in the human brain had arisen over more than a century of careful study of patients with brain lesions, most commonly acute stroke. Noteworthy early contributions came from people such as Paul Broca and Carl Wernicke for whom specific cortical areas related to language derive their names. Our objective was to examine language organization in the normal adult human brain, something that

[19] It is obvious that one could do a hypothesis-generating experiment first followed by a hypothesis-testing experiment but then the question arises, "How many areas of interest do you include in your analysis " As the number of areas increases, so does the required level of statistical significance. We used to refer to it as being "Bonferroni'd to death" after the Italian mathematician Carlo Emilio Bonferroni who proposed a method used to counteract the problem of multiple comparisons. His is considered the simplest and most conservative method but, unfortunately, deals a crippling blow to most complex imaging paradigms.

had been difficult, if not impossible, to do prior to the advent of modern imaging techniques. We began by asking how common English nouns are processed. How does the brain react when they are seen or heard? What is added when the seen or heard nouns are spoken? And, finally, what parts of the brain are engaged when one is required to consider their meaning? These questions resulted in a hierarchical paradigm in which, first, words seen or heard were contrasted with simply viewing a blank screen with central fixation point. Next, subjects were asked to say aloud the word they heard or saw, and these images were compared to just viewing or hearing the words. Finally, subjects were asked to generate a verb appropriate to the nouns heard or seen (e.g., see hammer, say hit).

Our PET imaging study of single word processing (Petersen, Fox, Posner, Mintun, and Raichle, 1988) provided a clear delineation of the cortical and subcortical networks involved in the different levels of single word processing. It also represented the culmination of 17 years of work in assembling the necessary imaging equipment and strategies to perform the experiments. It was a team effort with gratifying results. Much related work followed including the demonstration of cerebellar involvement in novel, high-level cognition (Petersen, Fox, Posner, Mintun, and Raichle, 1989); more detailed analyses of words and word-like symbols (Petersen, Fox, Snyder, and Raichle, 1990; e.g., pseudowords, consonant letter strings, and false fonts); and the effect of novelty on the organization of brain networks (Raichle et al., 1994). Gratifyingly, most of the findings and concepts enunciated in these early works have been amply confirmed in a large number of studies by others (for a recent comprehensive review of language studies with PET and fMRI see Price, 2012).

A Return to Brain Metabolism

One of my earliest contributions to our understanding of the relationship between brain function and metabolism was a study I performed in St. Louis prior to the development of imaging. It had long been assumed that activity-induced increases in blood flow were required to provide the added oxygen needed for an increase in brain energy metabolism. This belief was supported by data collected prior to my arrival in St. Louis showing that, in the resting state, blood flow and oxygen consumption were regionally correlated. With the techniques available to me in the Ter-Pogossian lab and a new probe system in the neuroradiology suite, we were positioned to test the hypothesis that blood flow and oxygen consumption would increase together to supply the added energy requirements of increased neuronal activity. Unfortunately we were unable to perform an experiment in normal persons because of the risks associated with the insertion of a needle into the carotid artery. However, we did have a subject in for evaluation of mild cognitive impairment who agreed to rhythmically squeeze an inflated blood pressure

cuff while we repeated his measurements of blood flow and oxygen consumption. Just as had been predicted, oxygen consumption increased with blood flow in the hemisphere contralateral to the active hand. Combining these data with the earlier studies in the resting state, we published our results in the *Archives of Neurology* in 1976 (Raichle, Grubb, Gado, Eichling, and Ter-Pogossian, 1976). For a number of years thereafter, this was my most cited publication. It troubled me, however, that our evidence that blood flow and oxygen consumption increased together during increases in brain activity was based on data from a single subject.

In the mid-1980s, Peter Fox and I decided to do the proper study with PET and validate our original observation that blood flow and oxygen consumption are correlated during changes in brain activity. We were certain that our results would confirm our earlier finding especially because that was accepted dogma. To our immense surprise, we could not replicate our original finding, try as we might with different stimuli (visual and somatosensory) and correcting for everything we could think of (e.g., venous contamination). Fortunately for what was to follow, we had done our homework with regard to our PET methods. They were, based on our earlier validation studies, giving us the correct answer.

We finally decided to present and publish our data. Oliver Lowry, the only member of the Washington University faculty who was a member of the National Academy of Sciences at the time, agreed to communicate our results to *Proceedings of the National Academy of Sciences* (*PNAS*). They were published in 1986 (Fox and Raichle, 1986), and the reaction was immediate, "The results couldn't possibly be correct." The criticisms, coming as they did from established figures in the field, seriously stifled discussion of the results at meetings. The reaction was particularly surprising given the fact that our finding was not novel.

In the early 1970s, a meeting was held at the Royal Danish Academy of Sciences under the auspices of the Alfred Benzon Foundation. The title of the symposium was "Brain Work: The Coupling of Function, Metabolism, and Blood Flow in the Brain." In attendance were all of the major researchers in the field. Also present were several others including me. Most noteworthy was a researcher from the Bearden Epilepsy Hospital in England by the name of Ray Cooper. He was involved in the use of electrocorticography to locate epileptic foci in the cortex of patients with intractable seizures. Because he was using bare metal electrodes, he took it upon himself to measure cortical oxygen availability at the same time. Depending on the location of his electrodes, he asked his patients to perform various tasks from simple motor movements to more complex cognitive tasks. His results were unambiguous; increases in activity of the cortex were accompanied by significant increases in oxygen availability, directly analogous to our later findings with PET. Surprisingly, there was no reaction to his findings of the sort we experienced. Not even comments about how to explain them.

Undaunted, we pushed forward with a second study. The question was whether glucose metabolism also failed to follow blood flow during increases in brain activity. In our 1986 *PNAS* paper, we actually speculated that blood might be acting alone. Surprisingly, that was not the case. In our second paper, published in *Science* in 1988 (Fox, Raichle, Mintun, and Dence, 1988), we showed again that activity-induced increases in blood flow significantly exceeded increases in oxygen consumption but, contrary to our expectation, glucose consumption increased in parallel to blood flow. This brought up the role of glucose metabolism outside of oxidative phosphorylation, so-called aerobic glycolysis, a subject to which I will return later in this chapter.

The most immediate consequence of our observation that blood flow changes exceeded those of oxygen was to provide a physiological basis for the emergence of functional magnetic resonance imaging, or fMRI.

The Emergence of Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) emerged as an important imaging modality on the basis of Paul Lauterbur's demonstration that, by combining classical nuclear magnetic resonance (NMR) with magnetic field gradients surrounding an object of interest, it was possible to create a 3-D image of the object. From this seminal observation emerged magnetic resonance imaging, or MRI.[20] The great strength of MRI was its superb ability to image soft tissues of the body, something that CT could not do. It was an immediate success in medicine. Also, it established itself as the technique for anatomical imaging of the brain, a role that it retains without rivals to this day. The idea that MRI could also image function was also present in the minds of many. The task was to find an MRI contrast agent that was sensitive to changes in blood flow. The first attempt at using an MRI contrast agent to look at changes in the brain was performed in the Martinos Laboratory of the Massachusetts General Hospital (Belliveau et al., 1991). They intravenously administered a paramagnetic contrast agent[21] that was sensitive to changes in blood flow and were able to demonstrate that MRI could be used in this way to monitor changes in brain activity. The problem with an administered contrast agent such as the one used at the Martinos Laboratory was that rapidly repeated measurements of the type being performed with PET and $H_2{}^{15}O$ were not possible.

The answer for MRI came from the Bell Laboratories and the work of Seiji Ogawa and colleagues. Seiji received his PhD from Stanford in nuclear magnetic resonance (NMR), working on the structure of hemoglobin.

[20] The term nuclear was dropped to avoid any association with ionizing radiation.

[21] The presence of a paramagnetic contrast agent reduces the strength of the MRI signal that can be detected in the MRI image. Because deoxygenated hemoglobin is paramagnetic, veins appear dark on an MRI image of the brain.

He continued to pursue research on hemoglobin at the Bell Labs. He was aware of the 1936 work of Linus Pauling on the magnetic properties of hemoglobin (Pauling and Coryell, 1936). In that work, Pauling and Coryell demonstrated that deoxyhemoglobin was paramagnetic. Based on this old observation, Ogawa posited that if blood flow increased more than oxygen consumption during increases in brain activity then the MRI signal would increase locally due to the reduced amount of deoxyhemoglobin present. He tested the idea by varying the concentration of oxygen in the air breathed by rodents in his MRI machine. As the concentration of oxygen was increased, the dark lines representing veins in the rodent brains disappeared. From this, he coined the term blood oxygen level dependent (or BOLD) signal, which has subsequently become synonymous with fMRI (Ogawa, Lee, Kay, and Tank, 1990). Because of its versatility and availability, MRI has become the tool of choice for mapping the function and anatomy of the human brain as well as those of laboratory animals from monkeys to rodents. Four studies appearing almost simultaneously in 1991 introduced fMRI BOLD imaging in humans (Bandettini, Wong, Hinks, Tikofsky, and Hyde, 1992; Frahm, Bruhn, Merboldt, and Hanicke, 1992; Kwong et al., 1992; Ogawa et al., 1992) and all embraced our earlier work (Fox and Raichle, 1986; Fox et al., 1988) as the physiological basis of BOLD imaging.

Imaging has become an increasingly important part of research in neurosciences, as well as the social sciences, and it is also an important face for brain research in the lay community. Using the search term "fMRI" PubMed presently finds more than 21,000 papers in the world's literature published since the introduction of fMRI in 2001. An additional 14,000-plus papers can be attributed to PET using the search terms "PET" and "brain." The thirst for information about brain function is universal, and imaging, for better or worse, has become a medium for the discussion.

A Paradigm Shift

Functional brain imaging, first with PET and now with fMRI, has followed a long tradition in neuroscience: studying neuronal responses to stimuli and activity during task performance. In this work, the role of bottom-up versus top-down (or feedforward versus feedback) causality is frequently discussed, reflecting a debate that extends back at least a century on the relative importance of intrinsic and evoked activity in brain function.

"Intrinsic activity" is ongoing neural and metabolic activity that is not directly associated with subjects' performance of a task. The distinction between intrinsic activity and task-evoked activity applies at many levels of neurophysiological examination, including events at the cellular level where ion channel proteins, receptors, and the components of signal transduction pathways turn over with half-lives of minutes, hours, days, and weeks (Marder and Goaillard, 2006). Brain imaging has recently entered this discussion with information that will likely be important in shaping

future research. It suggests to me an impending paradigm shift (Kuhn, 1996) brought about by surprising discoveries in imaging research that have occurred against a background of complementary work in electrophysiology and cell biology. I briefly review evidence that persuades me of this view.

Since the beginning of the 20th century and possibly earlier, two views of brain function have existed (for a comprehensive review, see Raichle, 2010). One view, pioneered by the early work of Sherrington (1906), posits that the brain is primarily reflexive, driven by the momentary demands of the environment. The other view is that the brain's operations are mainly intrinsic, involving the acquisition and maintenance of information for interpreting, responding to, and even predicting environmental demands, a view introduced by a disciple of Sherrington's, T. Graham Brown (1915). (For a review of his work in a modern context, see Yuste, MacLean, Smith, and Lansner, 2005.) The former has motivated most neuroscience research including that with functional neuroimaging. This is not surprising because experiments designed to measure brain responses to various stimuli and carefully structured tasks can be rigorously controlled, whereas evaluating the behavioral relevance of intrinsic activity can be an elusive enterprise. How do we adjudicate the relative importance of these two views in terms of their impact on brain function?

One means of evaluating the relative importance of evoked and intrinsic activity is to examine their cost in terms of brain energy consumption. In the average adult human, the brain represents about 2 percent of the total body weight but accounts for 20 percent of all the energy consumed (Clarke and Sokoloff, 1999). This high energy consumption occurs in the resting state—a behavioral state characterized by quiet repose either with eyes closed or open with or without visual fixation. During the resting state, subjects experience an ongoing state of conscious awareness largely filled with stimulus-independent thoughts (i.e., mind wandering or daydreaming). It is noteworthy that in rats and monkeys, the brain accounts for 2.4 and 5 percent of the energy consumed by the body, significantly less than in humans. Furthermore, relative to the very high rate of ongoing or "basal" energy consumption in humans, the additional energy consumption associated with evoked changes in brain activity is remarkably small, often less than 5 percent (Raichle and Mintun, 2006). This low figure likely applies to stimulus-independent thoughts as well. From these data, it is clear that the brain's enormous energy consumption is little affected by task performance, an observation first made more than 50 years ago (Sokoloff, Mangold, Wechsler, Kenney, and Kety, 1955; for prescient insights, see also Creutzfeldt, 1975).

What is the nature of this ongoing intrinsic activity that commands such a large amount of the brain's energy resources? Measurements of brain energy metabolism using magnetic resonance spectroscopy (Sibson et al., 1997, 1998; Shulman, Hyder, and Rothman, 2001; Shulman, Rothman, Behar, and Hyder, 2004) in a variety of experimental settings have indicated

that 60–80 percent of overall brain energy consumption is devoted to glutamate cycling and, hence, neuronal signaling. Complementary analyses using extant anatomic, physiologic, and metabolic data (Wong-Riley, 1989; Ames, 2000; Attwell and Laughlin, 2001; Lennie, 2003) to assess the cost of different components of excitatory signaling in the gray matter have arrived at similar conclusions. Such estimates leave for future consideration the demands placed on the brain's energy budget by the functional activity of inhibitory interneurons and glia (Magistretti and Chatton, 2005; Buzsaki, Kaila, and Raichle, 2007). That evidence notwithstanding, it is likely to remain the case that the majority of brain energy consumption is devoted to functionally significant intrinsic activity. The challenge, of course, is how to study these intrinsic brain processes. Functional brain imaging has provided some intriguing new insights.

Unmasking the Brain's Intrinsic Activity

Prior to our first published work on the subject, the idea that there might be an undiscovered network emblematic of the intrinsic organization of the brain simply did not exist. This network, now routinely dubbed the brain's default mode network (DMN) emerged from an entirely unexpected observation made during our early work using PET to map human brain function. In this work, we routinely included an eyes-closed or a simple visual fixation condition as one of the control conditions in our experiments. To some extent, this violated one of the canons of cognitive psychology in not controlling all of the variables in a control condition except the one of interest in the task itself. Whereas the control condition was simply resting quietly with eyes closed, it was clear that subjects were likely experiencing random thoughts unrelated to the experiment (i.e., mind wandering, daydreaming, or, more technically, stimulus-independent thoughts). Although we were very much aware of this "rule," many of our earliest experiments were based, for example, on the presentation of visual stimuli, comparing their properties or position in the visual field to the absence of the stimulus. It was not clear what the control for such an experiment might be other than the absence of the stimulus. Over time, of course, our experiments became ever more complex, as I have indicated earlier, including increasingly sophisticated tasks as well as control conditions. Being creatures of habit, however, we continued to include a simple eyes-closed rest or visual fixation condition in many of our experiments. In hindsight. I can think of no other rationale.

Because the purpose of early brain mapping experiments was to look for regional increases in brain activity, so-called "activations," the idea that areas of the brain other than those activated might reduce their activity was simply not considered and certainly not looked for. I do not recall when I first happened to look at the full spectrum of activity changes (i.e., decreases as well as increases) in subtraction images but when I did I was struck by

the fact that, when using visual fixation or eyes-closed rest as the control condition, the most prominent decrease was in the posterior cingulate and adjacent medial precuneus. Attracted by the striking nature of these task-induced localized decreases in activity, I began collecting examples among our many ongoing experiments, and I placed them in a file entitled MMPA for "medial mystery parietal area." A literature on this part of the cerebral cortex does exist, but it did not seem helpful in understanding our observations.

Several years after I began tracking the medial mystery parietal area, Gordon Shulman initiated a meta-analysis in our group of nine PET brain-mapping studies. His objective was to identify the network of areas comprising the brain's attention network. This study appeared in three publications, one of which (Shulman et al., 1997) featured a network of brain areas that decreased its activity in all nine of the studies making up the meta-analysis. The most prominent component of this network was the MMPA (i.e., the posterior cingulate cortex and adjacent precuneus), but it also included all that we have come to know as the brain's default mode network, or DMN (i.e., lateral parietal cortex bilaterally; dorsal and ventral medial prefrontal cortex; and medial temporal cortices).

The immediate response to the discovery of the DMN was a reminder from the scientific community that we had inadequately controlled for the ongoing mental state of our subjects and, therefore, could not interpret the results (for a review, see Raichle and Snyder, 2007). Our rejoinder (Raichle et al., 2001), published four years later and titled "A Default Mode of Brain Function," showed that the areas in questions (i.e., the DMN) were not activated during the resting state (i.e., the DMN did not exhibit the dissociation between blood flow and oxygen consumption typical of activated regions).

Creating a physiological distinction between activation and ongoing or intrinsic activity in a brain area or network of brain areas, based on quantitative measures of regional brain circulation and metabolism (Raichle et al., 2001), opened up a discussion of the importance of the brain's intrinsic activity that had been dormant for many years. Leading this discussion has been the brain's DMN, but the characteristic features of its intrinsic activity are shared by all other brain systems and their subcortical connections. This expanded view came to light through the rediscovery of an observation made many years ago that spontaneous fluctuations in cortical oxygen availability (so-called oxygen waves) exhibit patterns of spatial coherence (for a review of this early work, see Raichle and Mintun, 2006). At the time that these patterns were observed in experimental animals, the focus of the research was on the mechanics of capillary physiology (i.e., did capillaries of the brain exhibit spontaneous opening and closing that characterized capillaries in other vascular beds such as the lung?). Evidence against this hypothesis was, in part, that homologous areas of the cerebral hemispheres exhibited correlated fluctuations. The focus of this research was definitely

not on how this correlated activity might reflect a basic feature of brain functional organization. Once the argument was settled, these remarkable observations were largely forgotten.

As a graduate student at the Medical College of Wisconsin, Bharat Biswal was assigned by his thesis advisor, James Hyde, to investigate the origin of spontaneous "noise" in the fMRI BOLD signal. Prior to his work, this "noise" was removed from mapping studies by image averaging. During the course of his investigation, he and his colleagues asked if this spontaneous activity in one area of the cerebral cortex was correlated with activity in any other part of the brain. Choosing somatomotor cortex in one hemisphere, they immediately discovered that the spontaneous fluctuations in that area were strongly correlated with activity in the contralateral somatomotor cortex (Biswal, Yetkin, Haughton, and Hyde, 1995).

Much controversy surrounded Biswal's observation with concern that what he observed might be related to respiratory-induced fluctuations in CO_2 or fluctuations in cardiovascular dynamics (e.g., slow variations in cardiac output). We were aware of Biswal's observation but did not pursue its implications until Michael Greicius and colleagues at Stanford examined the pattern of spatial coherence arising from spontaneous fluctuations in the fMRI BOLD signal in the posterior cingulate and adjacent precuneus (i.e., a primary node of the brain's DMN) (Greicius, Krasnow, Reiss, and Menon, 2003). What they observed was the complete anatomy of the DMN. We were astonished! Almost overnight this observation galvanized our interest and that of others.

Studies of the brain's intrinsic activity using resting state fMRI BOLD imaging have become a dominant theme in human brain mapping (for review, see Fox and Raichle, 2007). By latest count, there are almost 3,000 papers on the subject on topics ranging from development to aging in health and disease. It is playing an increasingly important role in issues related to mental health where disorders of the intrinsic functional organization of the brain likely will be critical to their understanding and treatment. It is also becoming an important tool for presurgical planning and even intraoperative guidance (MRI scanners are appearing in increasing numbers in neurosurgical operating rooms). The DMN has remained central to this story, assuming a preeminent role in the brain's functional organization.

Metabolism, Development, and Disease

Brain metabolism has been a constant theme in my work, beginning with my indoctrination in the laboratory of Fred Plum and Jerry Posner through my studies of the origin of the fMRI BOLD signal and the identification of the DMN. Remarkably, for me at least, the theme continues with a focus on the role of glucose metabolism outside of oxidative phosphorylation (i.e., referred to as glycolysis or aerobic glycolysis depending on whether you are an endocrinologist or an oncologist, respectively). In my 1970 paper with

Fred Plum and Jerry Posner (Raichle, Posner, and Plum, 1970), our data revealed that aerobic glycolysis accounted for 10–12 percent of glucose metabolism. At the time, we took little note of this.

In my 1988 paper with Peter Fox, Mark Mintun, and Carmen Dense (Fox, Raichle, Mintun, and Dence, 1988), we observed that glucose metabolism increased with blood flow but oxygen consumption did not. Many discounted this as unimportant because of the small amount of energy produced by glycolysis alone. However others, particularly Pierre Magistretti and Luc Pellerin, pursued this lead and were able to show that glycolysis plays a critical role in the removal of glutamate from the synapse (Magistretti, 2011). Specifically, glycolysis fuels the Na^+/K^+-ATPase in astrocytes where glutamate is taken up along with sodium. Their work and that of others have shown that lactate may not only function as an alternate fuel source for neurons (now referred to as the "reverse Warburg effect" [Pavlides et al., 2010]) but also as a signaling molecule (for example, see Suzuki et al., 2011).

In 1994, Peter Lund Madsen and colleagues in Copenhagen reported that not only did glycolysis increase more than oxygen consumption during brain activation but that following the completion of the task glycolysis persisted for well over an hour despite the fact that blood flow and lactate production returned to control levels (Madsen et al., 1995). They suggested that one of the possible explanations was that glycolysis was participating in biosynthesis related to learning and memory, a hypothesis consistent with the well-known role of glucose in proliferating cell systems (e.g., in cancer where it is known as the Warburg effect after its discoverer). Consistent with this view was our much earlier work (Altman, Perlman, Volpe, and Powers, 1993; Powers, Rosenbaum, Dence, Markham, and Videen, 1998) and that of others (Kennedy and Sokoloff, 1957; Settergren, Lindblad, and Persson, 1976; Chugani, Phelps, and Mazziotta, 1987) on human infant metabolism, which showed that the newborn was remarkably glycolytic (approximately 30 percent of the metabolized glucose); that by age of two, the glucose metabolism of the developing human infant was already at adult levels and, by the end of the first decade, it was twice the adult level at a time of rapid synaptic proliferation in the developing brain.

All this prompted us to ask whether, in the adult brain, aerobic glycolysis was distributed uniformly or not. Nobody had ever bothered to ask that question. The results of the query were quite astonishing (Vaishnavi et al., 2010). Aerobic glycolysis was very nonuniformly distributed in the normal human adult brain. It was highest in the DMN and lowest in the cerebellum and the medial temporal lobes. And, although the DMN has a relatively high metabolic rate, it is second to the primary visual system where aerobic glycolysis is much lower than in the DMN. Thus, aerobic glycolysis is not a simple function of the overall metabolic rate of a brain region.

Following the discovery of the nonuniformity of aerobic glycolysis in the human brain, we have been trying to determine what functions it

is performing. The strategy we have chosen is to examine regional gene expression in the human brain in collaboration with the Allen Institute in Seattle and to determine on an anatomical basis what genes vary in their expression with the level of aerobic glycolysis. Our studies (Goyal et al., 2014) so far indicate that aerobic glycolysis correlates with gene expression typical of infancy and is related to synapse formation and neurite growth (i.e., transcriptional neotony). In contrast, regions with high rates of glucose oxidation (e.g., primary visual cortex) express genes that are related to mitochondria and synaptic transmission. Our findings are consistent with the view that "each neuron is constantly rebuilding itself from its constituent proteins using all of the molecular and biochemical machinery of the cell" (Marder and Goaillard, 2006), a view consistent with our recently published work on gene expression-based modeling of synaptic density in the human brain (Goyal and Raichle, 2013).

Finally, our work on the functional organization of the brain's intrinsic activity and its unique metabolic features has focused our attention on Alzheimer's disease. One of the pathological hallmarks of Alzheimer's disease is the accumulation of amyloid plaques in the brain. Several years ago, investigators at the University of Pittsburgh developed a PET-based radiopharmaceutical (Pittsburgh Compound B, or 11C-PiB) that binds to amyloid plaques (Klunk et al., 2004). One of the first revelations was that plaques accumulate preferentially in the DMN even before the onset of clinical signs and symptoms of the disease. One of the striking features of this association is the relationship between amyloid plaque distribution and the level of aerobic glycolysis (Vlassenko et al., 2010). This association between a unique brain network, its unusual metabolism, and the occurrence of Alzheimer's disease has opened up new ways of thinking about the pathophysiology of this dreaded disease.

Summary

It has now been 55 years since I entered the classroom of Dr. Dixie Lee Ray at the University of Washington. I was a junior majoring in history and political science envisioning a career in law like my father. I suddenly realized that there was a fascinating world of biology to be explored that I had never considered. The abrupt change in my career trajectory was a challenge, at times a bit frightening, but one that I have never regretted. The opportunities afforded me over the years have been extraordinary. The thrill of discovery remains undiminished.

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