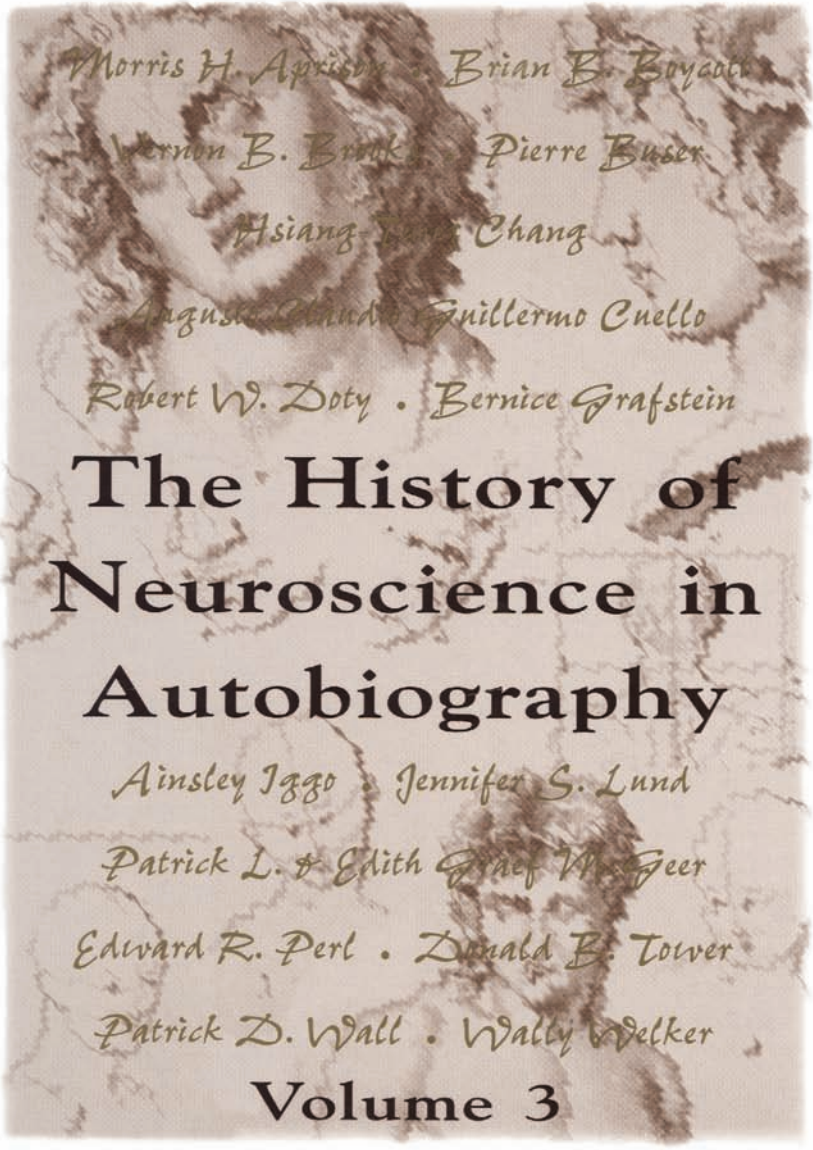

Edited by Larry R. Squire

The History of Neuroscience in Autobiography

VOLUME 3

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ACADEMIC PRESS

A Harcourt Science and Technology Company

San Diego San Francisco New York Boston London Sydney Tokyo

This book is printed on acid-free paper. ♾

Academic Press
A Harcourt Science and Technology Company
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
http://www.academicpress.com

Academic Press
Harcourt Place, 32 Jamestown Road, London NW1 7BY, UK
http://www.academicpress.com

Library of Congress Catalog Card Number: 96-070950

International Standard Book Number: 0-12-660305-7

PRINTED IN THE UNITED STATES OF AMERICA
01 02 03 04 05 06 SB 9 8 7 6 5 4 3 2 1

Contents

Donald B. Tower

Born:

Orange, New Jersey
December 11, 1919

Education:

Harvard College, A.B. (1941)
Harvard Medical School, M.D. (1944)
McGill University, M.Sc. (1948)
McGill University, Ph.D. (1951)

Appointments:

Montreal Neurological Institute, McGill University (1951)
National Institutes of Health, National Institute of Neurological Diseases and Blindness (1953)
Section on Clinical Neurochemistry (Chief, 1953)
Laboratory of Neurochemistry (Chief, 1961)
National Institute of Neurological Disorders and Stroke (Director, 1974–81)
Commissioned Officers Corps, US Public Health Service (1953). Assistant Surgeon General (RADM, 1975)

Honors and Awards:

Alpha Omega Alpha (1944)
Sigma Xi (1950)
John and Mary R. Markle Scholar in Medical Science (1951)
Distinguished Service Medal, US Public Health Service (1977)
46th Hughlings Jackson Memorial Lecturer, Montreal Neurological Institute (1980)
Honorary D.Sc., McGill University (1984)
Auszeichnung für Arbeiten zu der Geschichte der Justus-Liebig-Universität Giessen (1984)

Donald Tower trained originally as a neurosurgeon but turned to research, becoming a pioneer in neurochemistry. He investigated epileptogenic foci in the cerebral cortex of humans and experimental animals, demonstrating abnormalities in acetylcholine, glutamate, and potassium metabolism. Additionally, he carried out comparative studies of the neurochemistry of mammalian brains, with emphasis on the brains of the great whales. He was one of the three founders of the American Society for Neurochemistry and has written extensively on the history of neurochemistry.

Donald B. Tower

To compile a proper autobiography one must be a diarist or the equivalent. Most of us, myself included, did not pursue such a course and must rely on an imperfect memory plus collected reprints and various papers retained for other purposes. In my case I have been helped by the transcript of a series of autobiographical interviews taped by Louise Marshall (of the UCLA Brain Research Institute) (Tower, 1986) in 1986, when I was less forgetful than I am now. Besides the problems of remembering, there are family, many friends, and colleagues, and a host of others that one is not quite sure how to include in such an account. Our activities inevitably involve other people, often in interesting but very personal ways. Scientists traditionally minimize personalities and anecdotes, but I have tried to strike a balance between the extremes.

Beginnings and Education

My forebears came primarily from England and Wales and settled in New England. John Tower was an only child and ancestor to essentially all subsequent Towers in North America. He settled in Hingham, a Puritan community in the Massachusetts Bay Colony. His house still stands on the Main St. of Hingham. My paternal grandmother's family were Thompsons, originating from Wales. They arrived on the third embarkation of Pilgrims in 1622 or 1623. Through the Thompsons there were direct ties by marriage to Miles Standish, John and Priscilla Alden, and others. One of their direct descendents was John Thomas Zebediah Thompson, who was active in the Abolitionist Movement, maintaining a way station on the "Underground Railway" for escaped slaves en route to Canada. During the American Revolution, one of my ancestors in the Thompson genealogy, the Rev. Gad Hitchcock, preached revolutionary sentiments before the Legislature and British Governor Gage in the Old South Church in Boston. His son, Dr. Gad Hitchcock, served as surgeon in the Continental Armies.

My mother's family comprised principally the Bishops, from the Channel Island of Jersey via Connecticut to the Annapolis Valley of Nova Scotia as part of the New England Planters, who settled on the deserted Acadian lands in western Nova Scotia in 1760. There, my grandmother

Clara Bishop of Paradise, Nova Scotia, married Albert Jones of Clementsport, who was a descendant of Nicholas Jones who emigrated from New Jersey to Clementsport at the end of the American Revolution. Nicholas' wife, Catharine Ditmars, descended from several generations of Dowe Ditmars, whose forebears originated in Ditmarschen, a self-governing independent territory (thirteenth to the sixteenth centuries) in the Holstein area of southern Denmark and northern Germany.

My mother and father were married in March 1919. It was my father's second marriage; his first wife had died 2 years earlier. My two brothers were children of the first marriage and thus my half brothers. My early years were perhaps a bit out of the ordinary. I was born on December 11, 1919, in the Orange Memorial Hospital in Orange, New Jersey, and arrived home in Maplewood, New Jersey, on Christmas day. My father, originally a professor of economic geography (University of Pennsylvania and University of Chicago), served during World War I on the War Shipping Board in Washington, DC. He was a member of the delegation to the Peace Conference in Versailles, where he met Herbert Hoover, shortly appointed Secretary of Commerce in the Harding administration cabinet. Hoover asked my father to become commercial attaché at the U.S. embassy in London. Therefore, at the age of 20 months I sailed (in September 1921) with family on the HMS Adriatic to England and spent 30 months in Wimbledon in the Surrey countryside outside London. Here I must insert my first neuroscience notation. I have absolutely no recollection of the whole "adventure," including a full-time nanny, frequent trips to the nearby commons, summers at Southbourne (~~1~~922) and Le Zoute-Knocke-sur-Mer, Belgium (1923), and return at age $4\frac{1}{2}$ years to the United States in July 1924 aboard the S.S. President Harding. My first recollection was at Pocasset on Cape Cod (Massachusetts), where we summered until resettling in Maplewood. So much for early childhood memories.

The next year (1925) I entered kindergarten at the Jefferson Elementary School in Maplewood and continued into first grade the following year. I became the proud possessor of a copy of the *Bible*, presented to me for reciting the 121st Psalm at the Sunday School of the Morrow Memorial Congregational Church. That summer again at Pocasset I learned how to swim and to row a dory from my instructors: Shelly Pierce, Jake von Briezen, and Phil Rounds, each classmates of my brother Sheldon at Harvard College. Sheldon invited me to stay with him in Matthews Hall (where I later lived during my freshman year), where I met other classmates, notably Ted Ferris (later Rector of Trinity Episcopal Church in Boston) and Munroe Leaf (author of *Ferdinand*).

When in 1927 my father took a job with the Bethlehem Steel Company, we moved to Bethlehem, Pennsylvania. I was able to skip second grade and entered third grade at the local elementary school. My fifth grade year

was spent in Altadena, California, at the Thomas Edison School because my father was sent by his company to the California area. We lived with my maternal grandparents Albert and Clara Jones just a few blocks from the school. My grandfather had an extra lot next door where he grew various citrus fruits and other produce. It was Depression time, with hardships for many; grandpa and his neighbors took lug-boxes of excess free fruit to the local store for people to help themselves. I was impressed by the friendliness of my classmates, who elected me vice president of the class and put me in charge of a class project— building a scale model of Daniel Boone's frontier stockade at Boonesboro, Kentucky.

On our way home from California, we stopped in Arizona and New Mexico to see the Grand Canyon (extraordinarily impressive) and the American Indian pueblos along the Rio Grande River in New Mexico. Of special note was the visit to San Ildefonso Pueblo, where we met the famous potter Maria Martinez. I still have the beautiful black pot my mother bought from Maria in 1930. These experiences began my lifelong interest in the American southwest and its Indian tribes.

In the summer of 1930 we moved into our new summer cottage at Racing Beach, near Quisset Harbor between Falmouth and Woods Hole on Cape Cod. I enjoyed my first introduction to science in a practical laboratory course on freshwater and marine specimens—a course aimed at elementary school students and taught by the Marine Biological Laboratories at Woods Hole. In those days the marine and oceanographic institutions maintained an aquarium within the dockyard replete with seals and other sea life. The deep-sea research vessel *Atlantis* was often tied up at the dock. This same summer I took sailing lessons so that I could handle our small sloop and later crew on much larger boats.

Summers after 1930 were divided between Cape Cod and a boys' camp on Newfound (or Pasquaney) Lake in Hebron, New Hampshire. Camp Mowglis was founded in 1903 with themes drawn from Rudyard Kipling's *Jungle Books*. My older brother Sheldon had gone there in the early 1920s, and I was both camper (1931–1934) and counselor (1935–1939 and 1942–1943). Mowglis was a unique experience for me: I learned many new activities (camping, hiking in the White Mountains, canoeing, competitive swimming, rowing on a six-man crew, riflery, photography, and many more). Two activities stayed with me—rowing and photography. At Mowglis we rowed and raced in six-oared gigs. When I got to Exeter and to Harvard I graduated to eight-oared shells and even tried my hand at coaching while in college. I still own a rowing machine and work out almost every day. My introduction to photography coincided with the introduction of amateur 16- and 8-mm movie cameras, the development of color (Kodachrome) film, the introduction of 35-mm SLR cameras, etc. I became reasonably expert with Kodachrome color film and at Mowglis I became the camp photographer, making an annual record that could be used by

the director to attract prospects for the next season. I have continued to take photographs during travels and in the lab, and over the years I acquired literally thousands of Kodachrome slides and prints. I must mention the director of Mowglis during my years there: Col. Alcott Farrar Elwell, late of the U.S. Army—a great teacher and a wonderful person. I owe him many debts of gratitude.

Education continued into Liberty Junior High School in Bethlehem through the eighth grade. During this time, there were three items of interest: a very useful and practical course in shop, especially carpentry, drafting, and electricity; my first experience witnessing a grand mal seizure (by one of my classmates, with a good sympathetic explanation of epilepsy by the teacher); and a good course in geography, including the history of Pennsylvania and of Bethlehem (settled by the Moravians in 1741). My geography teacher Mr. Bear weighed more than 300 lbs. and was a strict disciplinarian, but he loved his subject and taught it well.

It was 1933, in the depths of the Great Depression and the first term of President Franklin D. Roosevelt's administration. My father was transferred to New York City to the American Iron and Steel Institute to help write the (National Recovery Act) code for the U.S. steel industry. He was chosen to administer the code and subsequently was elected president of the institute. Therefore, we moved to New York City, where I spent my ninth grade school year at Lincoln School, a so-called "progressive" school operated by Teachers College of Columbia University. It was an interesting year for me. No Latin was taught, and since I was eventually headed for Phillips Exeter Academy (in Exeter, NH) I tutored Latin privately. On the other hand, I had a valuable year of beginning French taught by a native French woman and a most entertaining year in the civics course. For the latter, the teacher took us on field trips to Harlem; Ellis Island; the packing-box dwellings of Hoover City (between Riverside Drive and the Hudson River); the Bowery, where we ate in Bernard McFadden's Penny Restaurants; and the Russian restaurant in Union Square. In those days New York was a more intimate, friendly city, but I was not destined to stay longer.

For the rest of my secondary school education I applied to Exeter and took the entrance exams. I flunked math and French, and received a D in English and a B in Latin. Therefore, much of my summer was devoted to tutoring with my mother (in math) and my older brother Jim (in French). The tutoring was successful; I passed the makeup exams and entered the lower middle (sophomore) year at Exeter. The school had recently installed the Harkness plan of instruction underwritten by a generous Harkness endowment and characterized by small classes seated at round tables with mandatory participation by every student. It was, and still is, a most effective system. I enjoyed it and did well scholastically and in extracurricular activities: music (glee club, choir, and orchestra), dramatics (I played Gramp Maples in Sherwood's *Petrified Forest* and a juror in Gilbert and

Sullivan's *Trial by Jury*), the French club "Les Cabotins," and crew and squash. My courses included languages, some math and physics, debating, and English. We had many visiting dignitaries; my favorite was the poet Robert Frost, who read a number of his poems and provided anecdotal footnotes.

College and Medical School

My college preference was Harvard, alma mater for my father and my two older brothers. There, I matriculated in 1937, living in Matthews Hall my freshman year and in the "gold coast" of Adams House as an upperclassman. We were privileged to have Raphael Demos and then David Little as house masters; my adviser was Richard Leopold, who became a lifelong friend. Adams consisted of several converted luxury apartments and included a swimming pool. I began with the idea of majoring in history (still a favorite subject), but during my sophomore year I realized that to pursue a pre-med course together with a history major I would have few, if any, opportunities for other courses. Therefore, I switched to major in chemistry and happily supplemented those courses with botany, zoology, Spanish, scientific German, several courses in history, philosophy, and anthropology (three courses). Extracurricularly, my principal activities involved crew and music. During my freshman and sophomore years I rowed on the 150-lb. or lightweight crews, where my contacts with coach Bert Haines and with the other crew coaches—Harvey Love (freshmen) and Tom Bolles (varsity)—made lasting impressions on me. Because chemistry labs encroached on afternoons I could not continue with varsity-level rowing but resorted to the intramural house crews. Adams House had one of the better crews and some of my closest friends, Joe Locke and Art Trott, rowed with me. During my senior year our crew needed a coach; I took on the responsibility with misgivings, but our crew raced well.

For music, I tried out and was accepted for the Harvard Glee Club then directed by G. Wallace Woodworth. "Woody" was a fine teacher and choral director. We sang at many nearby colleges, gave campus concerts, and had an annual performance with the Boston Symphony Orchestra, then directed by Serge Koussevitsky— a truly great musician. My crowning experience was singing with the Harvard Glee Club and the Boston Symphony a mighty work of music: Beethoven's *Missa Solemnis*. It was a special occasion marked by recordings by RCA Victor during three performances in Boston's Symphony Hall. A copy of the recording is in my files.

The compelling memories of my college years regard my courses in chemistry and in anthropology. Qualitative and quantitative analyses made something of a chemist out of me, but the course in organic chemistry taught by Louis Fieser was outstanding. Fieser and his wife Mary

were in the forefront of the newer aspects of organic chemistry, notably the natural products and carcinogens related to phenanthrene. There was no textbook; Fieser promised that if we took good notes, we would have a good, complete text by the end of the course. Another outstanding course was on industrial chemistry taught by Grinnell Jones. Much of the course involved field trips to various industrial sites ranging from a municipal water purification plant to soap factories, oil refineries, sugar refineries, and more. We were required to write a detailed report, complete with flow sheets for each industrial process.

In anthropology, I took courses in physical anthropology from Earnest A. Hooten, cultural anthropology from Carleton S. Coon, and archeology from J. O. Brew. These scholars and their colleagues were in the forefront of the field at that time. For archeology, I did a study for a term paper that led to my first scientific publication. In the Peabody Museum at Harvard were collections of artifacts gathered from various excavation sites, many of them in the American southwest. A notable feature of these collections was the prevalence of jewelry and ornaments fashioned from marine shells, especially in prehistoric sites in Arizona and New Mexico far from the marine origins of such shells. Certain species had habitats restricted to the Pacific coast or to the Gulf of California or the Gulf of Mexico, suggesting discrete trading routes from marine origins to bejewelled wearer. Since the Harvard museum of comparative zoology had sizable collections of molluska, it was possible to compare the archeological shell jewelry and in many cases identify the species of marine organism. Malacology—the study of shells—was well represented at that time. I was indeed fortunate to work with a budding young malacologist, R. Tucker Abbott, who later made a distinguished career in the field. As a result I was able to suggest probable trade routes to the southwestern sites. At J. O. Brew's suggestion I wrote up the study and published it in the *Papers of the Excavators' Club* in 1944 (Tower, 1945).

After 4 years of college I graduated with the class of 1941 with an A.B. degree *cum laude* (in general studies). I had already applied to several medical schools, with the Harvard Medical School as first choice. The head of admissions, Asstant. Dean Worth Hale, interviewed me; he had the disarming habit of closing his eyes while I answered his questions and one did not know whether he was listening or asleep. Nevertheless, I was accepted and the system seemed to work since all those accepted into my class graduated. My choice of medicine as a career was made before my secondary (Exeter) school years. It was rather taken for granted, despite the fact that I had no medical or scientific members of my immediate family. My father and two older brothers were business oriented. Only later did I find that I had two medical cousins, daughters of my father's older brother William, namely, Elizabeth Tower Troy, a psychiatrist in practice in Chicago, and Sarah Tower Howe, a distinguished

neuroanatomist at Johns Hopkins in Baltimore, and later a psychiatrist at the Pratt Clinic in Baltimore.

Here, I interpolate a brief account of my last two summers before entering the Harvard Medical School. At my father's suggestion I had planned trips to Europe, but the outbreak of World War II precluded such travel. Instead, I planned travel to western parts of the United States and Canada, including many national parks: Bryce, Zion, Grand Tetons, Yellowstone, Glacier, Waterton Lakes, Yoho, and Jasper. The last two were included in a 1940 pack trip led by Will and Dorothy Torbert (of Mamaroneck, NY) and organized for high school and college students during their summer vacations. We traveled by horseback through northern Jasper Park (on the Alberta-British Columbia border). There were 10 of us, plus 5 hands (guide, packers, wrangler, and cook), and approximately 20 packhorses with tents and supplies for the 3-week trek. We enjoyed magnificent scenery, saw moose and mountain goat, fished successfully for trout, and ended our trip at Mount Robson, the highest peak (13,000-plus feet) in the Canadian Rocky Mountains. As an introduction to travel and sightseeing it would be difficult to surpass this trip.

The following year I joined the Torberts for a trip to Monument Valley and Rainbow Bridge on the Arizona–Utah border in the Navajo Indian Reservation. Here, I resumed my interests in American Indians, especially the Navajos, who comprise the largest tribe and live on the largest reservation in the United States. We made our headquarters at Goulding's Trading Post in Monument Valley. The trading post was founded and operated by Harry Goulding and his wife "Mike" and was situated a few miles north of Kayenta, where the original traders to the Navajo, John and Louisa Wetherill, had their trading post. Part of our trip involved a visit to Rainbow Bridge (National Monument)—an all-day ride on muleback down the canyons, overnight at the bridge, and an all-day muleback ride out. Today one can visit the bridge by boat up the Colorado River from Glen Canyon Dam and Lake Powell, but in 1941 the only access was the long, hot muleback ride. Rainbow Bridge is the largest known natural bridge in the world (height 309 feet, span 274 feet), large enough to accommodate the Capitol building in Washington, DC, beneath it. The first white man to see the bridge was John Wetherill, who later guided President Theodore Roosevelt to it. From 1910 up to our visit in 1941, only approximately 3000 people had registered as visitors to the bridge. Both the bridge and the natural buttes or monuments in Monument Valley are most spectacular. During our sojourn at Goulding's we attended a 3-day Navajo "sing" or healing chant attended by many hundreds of Indians. We also met a party of photographers that included Joseph Muench and Ansel Adams. It was easy to understand the attractions. Clearly, I had succumbed to travel and to recording its sights photographically.

By the autumn of 1941, in the United States war seemed imminent. My medical school class was the first to convert the 4-year course into 3 years by eliminating holidays and vacations. Therefore, we became the class of 1944. Shortly after Pearl Harbor we went on a full wartime footing. In January 1942 all but a handful of my class joined either army or navy reserves. The navy was my choice; I was commissioned an Ensign H(V)P until July of 1943 when the army ASTP and navy V-12 programs were begun. Then we were ordered to active duty, put in uniform, had our tuition and expenses paid by the armed services, and were even paid a small monthly allowance. In retrospect, the military or naval aspects of our lives seem minimal (although at the time we perhaps thought otherwise). We were indeed immersed in learning medicine almost to the exclusion of anything else. There was an exception for weekends during July and August of 1942 and 1943 when I took the late Saturday train to Plymouth, New Hempshire, where the camp Mowglis car picked me up. On those Sunday mornings I conducted the weekly health exams of the campers and tended to other medical chores since it was impossible for the camp to recruit regular medical counselors because of the war. The camp was served by the neighborhood M.D. but I handled much of the routine care. Late on each Sunday I returned by train to Boston.

Traditionally, the first 2 years of medical school were mostly preclinical: gross and microscopic anatomy, physiology (taught in his final year by Walter Cannon, assisted by Arturo Rosenblueth and Joseph Hawkins), biochemistry (with Baird Hastings and colleagues), bacteriology (under John Enders and William Hinton), and pharmacology (with Otto Krayer). I should not ignore our introductions to clinical areas: Physical diagnosis included cardiology by Mark Altschule (who demonstrated anginal attacks elicited by step climbing) and the many aspects of rheumatic hearts at the Good Samaritan Hospital under T. Duckett Jones. Also, we had an elective course on dog surgery given by Carl Walter. Despite contrary attitudes, this course was invaluable in teaching us anesthesia, tissue handling, various standard surgical procedures, and postoperative care. It was expected that our dog would survive in good condition; certainly our beagle did and greeted us affectionately throughout the course. I know of no adequate alternative for providing an introduction to clinical surgery.

We were taught gross anatomy by Robert M. Green, who demonstrated the lesson for the week, and then Allan Graflin supervised our cadaver dissections. I enjoyed anatomy and was privileged during my second year to be chosen prosector, whose responsibility it was to prepare Professor Green's cadaver for the class lecturedemonstration. My own predilection was biochemistry. Baird Hastings and I became good friends over succeeding years. At that time he led a research team studying hepatic carbohydrate metabolism *in vivo*. The radioisotope tracer substrates were

prepared by the cyclotron at MIT across the Charles River in Cambridge and were rushed with police escort and sirens screaming to the Harvard Medical School (HMS) biochemistry labs for syntheses and injection into the experimental animal. These were remarkable experiments, especially considering the short half-life of the radioisotopic label. We could not participate directly in these experiments, but the results were reported in our lectures. I did attempt a small research project under Hastings—an attempt to adapt thiochrome, the fluorescent derivative of thiamine, for a serum assay for the vitamin. Pilot experiments worked but wartime shortages of storage batteries (to operate the fluorometer) prevented a definitive study.

At the end of our lab in biochemistry we conducted a class experiment, reproducing the recent studies on thiamine deficiency in pigeons reported by Rudolph Peters (later Sir Rudolph) at Oxford. The deficient pigeons developed ataxia and opisthotonus, and they rapidly became moribund. An intramuscular injection of thiamine cured these birds within minutes (Fig. 1). We also did cocarboxylase assays on the brains of deficient birds, demonstrating failure of the enzymatic step and its reversal upon *in vitro* addition of thiamine. It was these studies that led Peters to his concept of the biochemical lesion (Meiklejohn *et al.*, 1932). Today these studies are ancient history, but in 1942 this was new and exciting. It is of interest that we conducted the brain enzyme studies in what had been Otto Folin's lab at the McLean Hospital (in Belmont, MA), then headed by Elmer Stotz and in a few years to be taken over by Jordi Folch-Pi. One brief footnote: A graduate student, Christian Anfinsen, was then carrying out his doctoral research in the department on the effects of postnatal blinding on retinal acetylcholinesterase activity measured by the Cartesian diver technique. We later did some work together at the National Institutes of Health (NIH).

Physiology and pharmacology complemented biochemistry. Cannon did not lecture well but his assistants Rosenblueth, Hawkins, Hallowell Davis, etc. made up for him. I have two vivid memories: recording our own electrocardiograms and electroencephalograms on the original string galvanometer instruments built by Alexander Forbes and Hallowell Davis and introduction to blood gas analyses with the Haldane and Van Slyke apparatuses, as taught by Joe Hawkins. Also, we interacted when I was at the NIH and he was first at Merck and then at the Kresge Institute in Michigan. Nevertheless, much of our physiology was acquired in Otto Krayer's course in pharmacology. Krayer was a very precise, Germanic lecturer, but his laboratory demonstrations mounted by his assistant Gordon Moe were fabulous. Cross-circulation experiments to demonstrate cardiorespiratory physiology and pharmacology were usually prepared in duplicate pairs in case problems developed. As I recall, they never did. At the end of medical school, each class elected a most admired professor. Our class chose Otto Krayer.

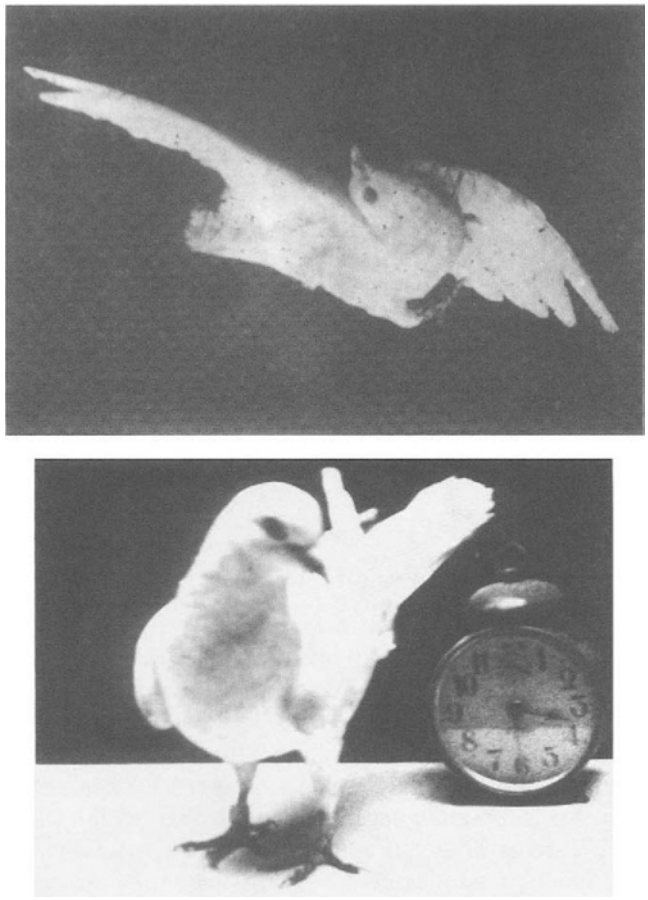


Fig. 1. Reproduction of Peters' experiments on thiamine deficiency in pigeons. (Top) Pigeon at the height of dietary deficiency, exhibiting opisthotonus (at about 10–12 diet days). (Bottom) The same pigeon 90 min after i.m. injection of 25 μg of thiamine (from movie taken by Tower during 1942 experiments at Harvard Medical School).

The clinical years brought us to the threshold of being M.D.s. I came away with a firm emphasis on the nervous system and neurology. Our introduction was the second-year course in neuropathology taught by Stanley Cobb. He achieved many converts, and we were further influenced by Derek Denny-Brown and Houston Merritt at the Boston City Hospital and by Franc Ingraham, pediatric neurosurgeon at the Children's Hospital and in Elliott Cutler's wartime absence also neurosurgeon at the Peter Bent Brigham Hospital. Denny-Brown stands out for the superb bedside teaching demonstrations that created a virtual textbook of neurology. Merritt went on to Columbia University College of Physicians and Surgeons (P & S) in New York City to introduce, with Tracy Putnam,

Dilantin (phenytoin) for treatment of seizures. With lngraham I had my first introduction to contemporary neurosurgery the successful excision of a huge frontal lobe meningioma, in four stages. Ingraham privately developed and equipped research labs, where studies on primates to delineate the blood–brain barriers and the exchange of fluids and solutes across them had their origins in experiments by Donald Matson (later at the Mayo Clinic), Bertram Selverstone (later at the New England Medical Center), Edgar Bering (later at NIH), and others. During my senior year I spent an elective month with Shields Warren.

Medical school ended all too soon, in September 1944. We marched in uniform in the HMS quadrangle and received our diplomas awarding us the M.D. degree and also our commissions as medical officers in the army or navy. Some of us, myself included, were recognized by election to the honor medical society Alpha Omega Alpha. Civilian internships were encouraged by the armed services, so most of us went on inactive duty to begin interning.

Internship and U.S. Naval Service

For now obscure reasons I favored a straight surgical internship with Owen Wangensteen at the University. of Minnesota Hospitals in Minneapolis. Having been accepted elsewhere, I importuned Wangensteen by telegram to accept me. I began on Donald Creevy's urology service with Frank Roach as resident. It was a good beginning, and I learned much about "doctoring." Then I moved to Wangensteen's service, which averaged about 60 patients, mostly gastrectomies (for ulcer or tumor), all the responsibility of the chief resident David State and one intern (wartime shortages precluded more personnel). We were in surgery every weekday for two or three gastrectomy procedures; meanwhile, new patients arrived needing histories and physical exams, and all postoperative patients were on Wangensteen gastric suction that necessitated intravenous fluid replacement therapy. One learned a great deal, but it was an exhausting couple of months. The highlight of my year was the rotation through the neurosurgical service under William T. Peyton. Originally an anatomist, he had been recruited to establish the neurosurgical service. He amplified his teaching skills with the neurosurgery. I had a special learning experience because Donald Simmons, the resident, contracted hepatitis and was hospitalized as I began my last rotation. Peyton appointed me acting resident, and when he was satisfied that I knew what to do, he left the surgery to me while he remained on-call in his office. Thus, I performed sympathectomies by the Smithwick technique (then very much in vogue for hypertension, tachycardia, and the like), evacuation of subdural hematomata through burr holes, most operative closures, etc. Of course, for more difficult or complex procedures, such as a posterior fossa exposure

for acoustic neuroma, Peyton did the surgery and would delight in calling the nurses and interns in the gallery to come down and observe over his shoulder while he gave a succinct demonstration of the anatomy exposed to view. What a fabulous neurosurgical experience:

At the end of my internship I received orders to active duty as a lieutenant (junior grade) in the Medical Corps of the U.S. Naval Reserve [Lt. (j.g.), MC, USNR] and was directed to report to the Great Lakes Naval Hospital in Waukegan (near Chicago), Illinois. Great Lakes was an enormous hospital complex housing about 20,000 patients. When reporting in I tried to tell the WAVE yeoman behind the desk my qualifications in neurosurgery but was assured that they had plenty of neurosurgeons as she assigned me to a large internal medicine ward filled with personnel awaiting disability discharges. Just as I left Great Lakes I happened upon the bulging neurosurgical wards where the sole neurosurgeon told me how much he needed help.

My new orders were to proceed via San Francisco to report to the Commander, Seventh Fleet, which was in the western Pacific and destined for the initial invasion of the Japanese island of Kyushu. Had it occurred, it would have been far more devastating in casualties than the Normandy invasion. By the time the navy found ship transportation for me the war was over, but I and thousands of others went anyway—such was the ponderous pace of the system adjusting from a wartime to a postwar footing. I sailed on the attack transport General William Mitchell (carrying 5000 new naval recruits) to arrive at Samar on Leyte Gulf in the Philippine Islands in September 1945. The confusion was great as more and more recruits like me kept arriving to overload the receiving station at Samar. After some weeks I received new orders to report to the naval operating base (USNOB) at Subic Bay on the Philippine island of Luzon, north of Manila and the Bataan Peninsula. I had very little status for air transport priorities until I found that the transportation officer was Tom Bolles, erstwhile varsity crew coach at Harvard. I caught an early flight via the island of Negros to Manila, where I obtained passage on landing craft infantry (LCI) bound for Subic Bay. When I reported to the base medical officer, he said, "What are you here for?" After Capt. Youngkin and Capt. Summers and the Executive Officer Lt. Fechter deliberated, it developed that I must be the new preventive medicine officer. That assignment provided me with an office, a Jeep, a malaria control unit, and an epidemiology unit [combining venereal disease (VD) and malaria components].

Immediately I was asked to inspect and approve the new water purification system for the naval base (population 8000–10,000) and the civilian community outside it (population 19,000–20,000). Had I not had my industrial chemistry course at Harvard College I might have been at a loss over such a technical matter. Fortunately, I remembered most of it as I viewed

a rather sophisticated system designed to supply filtered and chlorinated water to the entire community. There was one major flaw: The wooden chlorination tank was sheathed in sheet lead (to protect the wood). I demonstrated to the engineers the dissolution of sheet lead in the chlorine solution. Therefore a wooden tank lined with cement sheathing was substituted and base personnel—naval and civilian—were spared an outbrak of lead poisoning.

The facility at Subic was acquired at the end of the Spanish–American War as an extensive naval reservation encompassing most of the protected harbor bay (except for Subic City and environs) and extending to the ridges of the mountain peaks behind. In October 1945 it consisted of a submarine base and degaussing station (under separate commands) across the bay, the naval base and supply depot (approximately 8000 strong), and the civilian city of Olongapo of nearly 20,000 native Filipinos. The entire public health and preventive medicine responsibilities devolved on me. Aside from the usual VD control, the principal public health problem was malaria—endemic in the native population and spread by *Anopheles flavirostratis* as its indigenous vector breeding in the mountain streams of the naval reservation.

Considering the malaria problem, we wondered if treating the host population of native inhabitants with atabrine (then the preferred prophylaxis for malaria) would reduce the availability of malarial parasites to the *Anopheline* vector. We had the laboratory and field facilities available, very ably supervised by Lt. R.G. Harwell, USN, and Chief Pharmacists Mate W. W. Goble. Mosquitoes were trapped and species distribution and prevalence were established by our entomologists (Filipinos trained by the U.S. Navy). Blood smears for parasite levels were taken by our parasitologists (also Filipinos trained by the navy) on 20–30% of the Olongapo population. I ascertained spleen indices on most of the children in the community. Also, we arranged for intensive oiling treatment of accessible streams plus aerial spraying (from the naval air station at Sangley Point, Cavite, Manila Bay), with droplet monitoring of the applications. The precise population of Olongapo was established by a complete census, and the city was divided into its barrios, each with a supervisory warden and wardens for each block or section of the barrio. Administration of atabrine was done under direct supervision by the block warden and checked off each day. Additional supervision was provided by Dr. Daniel Labrador, a civilian Filipino physician assigned to Subic Bay. It was possible to do all this because the Filipino residents lived within the naval reservation and were subject to its regulations. However, we had also enlisted the approval and support of the Philippine Minister of Health.

Actually, the project proceeded very well, with a minimum of side reactions to the atabrine, a maximum (essentially 100%) compliance, and a significant drop in the demonstrable malarial parasitemia after the

month-long treatment period. Thus, the feasibility and reduced parasite availability were demonstrated. One additional plus was obtained. In the midst of the atabrine trial we received word that a tidal wave from a mid-Pacific earthquake was to be expected. The terrain at Subic Bay installations was essentially at sea level so the naval command ordered total evacuation to the surrounding hills. Our block warden system was pressed into service to alert all civilians and to ensure full evacuation. Fortunately, no tidal wave arrived, but the organization worked remarkably well. The atabrine project was written up in detail with maps, photographs, and statistics, but it was deemed a "restricted" document, not for public view at the time. In a sense it is my second career scientific publication (Tower, 1946).

In September 1946 I was relieved of my duties and ordered home to revert to civilian life. I had tried to defer departure in order to secure more follow-up data on the atabrine study, but the navy was very firm that I was no longer needed. As noted later, 7 years later the navy informed me than I still owed 2 years of active service. From Subic Bay I sailed on a navy attack transport via the great circle route along the Aleutian Islands chain to San Francisco. In mid voyage the ship's medical officer convened a meeting of the 20-odd passenger medical officers to handle a crew case diagnosed as acute appendicitis. Being a dermatologist, the ship's medical officer wanted to defer to one of us passengers with more surgical experience to do the appendectomy. It developed that I was the only one with the qualifications and so I was elected. Now, who was to administer the open-drop ether anesthesia? Again it turned out that I was the only one with experience (at Harvard we were required to administer 12 anesthetics under supervision in order to graduate). It was decided that I would give the anesthetic and direct the ship's doctor over the anesthesia tent on removal of the appendix. The Pacific was rough that day, so the ship's captain hove the vessel to during the surgery. Under the circumstances the procedure took longer than expected, and the captain kept phoning from the bridge to know when he could resume course and speed. The appendix proved to be quite normal; the young seaman made an uneventful recovery.

En route home I stopped in Minneapolis to visit Dr. Peyton and, I hoped, to secure a slot in his neurosurgical training program. Peyton assured me that he expected to accommodate me eventually, but so many trainees had returned home earlier that there was a waiting list of several years. That did not solve my immediate problem; I asked for suggestions. Peyton recommended that I apply to Dr. Wilder Penfield, director of the Montreal Neurological Institute (MNI) in Montreal, Quebec, Canada. Somewhat to my surprise, I was accepted to begin training on the first of January 1947. I drove from my Connecticut home through subzero temperatures in Vermont and Quebec to arrive at the doors of the MNI on New Year's Day

1947. Of course, it was a holiday, and except for patient care staff hardly anyone was there. The exception was Dr. William C. (Billy) Gibson, now in Vancouver. He welcomed me, gave me a tour of the facilities, helped with my housing needs, and generally extended a warm and generous welcome.

Montreal and the MNI

The immediate post-World War II period was a golden era at the Montreal Neurological Institute. At a time when neurological and neurosurgical training was at its lowest ebb in North American and European centers, two facilities bridged the gaps. The MNI rapidly expanded its training programs, attracting a mature cadre of trainees and researchers worldwide. Later, the U.S. Veterans Administration (VA) initiated a neurological training program at various of its medical-school-based VA hospitals. VA neurology was under the direction of Pearce Bailey, fresh from U.S. Naval Service. Literally speaking, these two programs (MNI and VA) resurrected American neurology from its nadir and began the rebuilding. The MNI had been opened in 1934 with a Rockefeller endowment and an affiliation with the McGill University Medical Faculty and the Royal Victoria Hospital. The MNI consisted essentially of two units: a neurological/neurosurgical hospital originally with four wards totalling about 150 in-patients, plus all the usual patient services and facilities, and three or more floors of research laboratories in the various neuroscientific disciplines. The entire facility was housed in an eight-story building across from the Royal Victoria Hospital (to which it was connected by an over-the-street bridge) and up the street from the McGill campus and medical school.

When I initially met with Dr. Penfield he stressed a basic tenet of the MNI training program: to combine clinical care with laboratory research. Each senior clinical staff member shared this philosophy by heading a ward service and by supervising a research laboratory. In view of my background in chemistry, Penfield proposed that I spend a year or so doing a research project in the Neurochemistry Laboratory, staffed by Donald McEachern as director and chief of the MNI Neurology Service and by K. A. C. Elliott, recently recruited as full-time neurochemist (incidentally, the first anywhere in the field to be so designated). The idea appealed to me. I liked Penfield, whom I came to value as a close friend. He was a dedicated clinical scientist, at the forefront of developments in the fields of epilepsy and cerebral localization. He succeeded marvelously well in turning the vision of a clinical research institute into an internationally famous center.

During my 6 1/2 years at the MNI there were many trainees (fellows) from distant lands; they were friends and colleagues and eventually became leaders in their own countries: Kristian Kristiansen from Oslo,

Norway; David Ingvar from Lund, Sweden; and Otto Magnus and Jan Droogleever-Fortuyn from The Netherlands; Aloys Werner from Geneva, Switzerland; Jerzy Olszewski and Igor Klatzo from Poland via the Vogts' Institute in Germany; Cosimo Ajmone-Marsan from Torino, Italy; Fuad Haddad from Beirut, Lebanon; Allan Byrd from Johannesburg, South Africa; Jacob Chandy (at Vellore) and Ram Ginde (at Bombay) from India; Choh-luh Li from Shanghai; John Hunter from Sydney. Australia; Victor Reyes from Manila, Philippines; and Arlindo Conde from Sao Paulo, Brazil. In addition there was a host of Americans and Canadians: Arthur Ward in Seattle; John Hanbery at Standford; John Myers in Detroit, then Houston; Lamar Roberts in Gainesville, Florida; Alfred Pope at the McLean Hospital in Belmont, Massachusetts; John Lord in Bethesda, Maryland; Milton Shy and Maitland Baldwin in Denver, then NIH in Bethesda; Clarence Green in Washington, DC (the first board-certified black neurosurgeon in the United States); Theodore (Ted) Rasmussen in Chicago, then Montreal; William Feindel in Saskatoon, then Montreal; and many more. Some of them, including Chao Yi-cheng (a 1939 trainee) were pioneers in establishing neurosurgery in their native countries: Chao in China, Chandy in India, Haddad in the Middle East, and Kristiansen in Norway. Such samplings may give some idea of the wealth of contacts and exposures that the Montreal years provided.

It was proposed that I research the role of the excitatory neurotransmitter acetylcholine in epilepsy. Epilepsy research, care, and treatment were major programs at the MNI, centered largely around Penfield's program of surgical excision of epileptogenic (seizure) foci from accessible brain areas. Since Penfield's cases were done under local scalp anesthesia only, with the patient awake and responsive to the surgeon, cerebrocortical stimulation and localization were studied and the electrical activity (ECG or electrocorticogram) of the exposed cortex was monitored by Herbert Jasper, head of the EEG and neurophysiology laboratories. Acetylcholine was just coming into prominence as a result of the studies by Sir Henry Dale and by Otto Loewi characterizing it as a neurotransmitter and by the many British studies by Wilhelm Feldberg and colleagues and by Judah Quastel on physiology and metabolism.

How to proceed? We decided to begin with studies on cerebrospinal fluid (CSF) sampled from interictal and ictal patients as well as nonepileptic "controls." The standard assay for acetylcholine (ACh) was by measuring the contraction of the dorsal muscle of the leech *Hirudo medicinalis*, but it seemed too insensitive for assaying CSF. However, John Henry Welsh at Harvard had just published a method using the isolated heart of the clam or quahaug *Venus mercenaria* that provided the desired degree of sensitivity. I corresponded with Welsh, found a source for the clams (at the MBL in Woods Hole, MA), and set up an assay involving inhibition by ACh of the isolated beating heart—the degree of inhibition being a function of the

concentration of ACh in the prostigmine-preserved samples. The identity of the inhibitor ACh was ascertained by appropriately inactivated samples. There had been isolated reports of ACh in CSF from seizure patients, but ours was the first extensive investigation. Not only were the assays for ACh positive for seizure patients but also the concentration of ACh seemed to be a function of the frequency of seizures and the juxtaposition of CSF sampling to the occurrence of major seizures. Control (nonepileptic) samples were all negative except in two special circumstances: in the early days after a head injury and in the early intervals after electroshock therapy in psychiatric patients. The latter study evolved from the craniocerebral trauma cases by arguing that electroshock might also be regarded as a form of *commotio cerebri*. I had examined the cholinesterase (ChE) activity in the CSF out of concern for its possible influence on ACh in CSF. With the exception of the trauma and electroshock cases, the activity of ChE (total and AChE) was so low that it had no influence on the levels of ACh. For the trauma samples the activity of butyrylChE was markedly elevated immediately after trauma. These studies were published (Tower and McEachern, 1949), and subsequently confirmed by others. Somewhat unexpectedly, I learned that the study qualified me for an M.Sc. degree from McGill University, which was awarded in mid-1948. At that point I suspended research to go on the wards as assistant resident in Neurosurgery on the service, jointly supervised by Wilder Penfield and the MNI's third neurosurgeon Arthur Elvidge.

At this point I must insert a major new personal development. Shortly after my arrival at the MNI I met Arline Croft, R.N., Assistant Head Nurse on the second floor ward housing most of Dr. William Cone's surgical patients. We became engaged and were married in her hometown of Chester, Nova Scotia, on August 5, 1947. This was a most happy event and as I write 52 years later a most successful union. In 1951 we welcomed our daughter Deborah Alden Tower, now married to Steven A. Fretwell and with two children, Kelsey Alden Fretwell and Lucas Tower Fretwell, our enjoyable and talented grandchildren. My marriage to Arline Croft introduced me not only to a great second family but also to Nova Scotia and especially to Chester and its environs. As I sit writing in the living room of Avis Croft Karlsen,[1] Arline's sister, looking out on the Front Harbor and the sailing yacht races at Chester, I recall the many summers of sailing, swimming, golfing, photography, and more that have made Chester and Nova Scotia a cherished second home.

I spent the year of 1948–1949 in the neurosurgical residency program. I still marvel at the many tours-de-force carried out by Arthur Elvidge:

[1] With deep sadness, I must record Avis Karlsen's death in late August 1999 at the age of 80.

massive glioblastomas, formidable arteriovenous malformations, and horrendous head injuries with compound skull fractures. A high percentage of these cases survived and prospered—a tribute to Elvidge's surgical skills and unorthodox approaches to many of these seemingly impossible problems. However the crux of my residency year was the exposure to Penfield's surgical treatment of cortical epileptogenic foci. These were long operations, largely because of the observational studies carried out by Penfield on the exposed cerebral cortex. Because the patients were awake, Penfield could examine by gentle electrical stimulation the extent of the focus, often reproducing aura or seizure patterns as described by the patient and observers, together with the electrocorticographic recordings from the surface of the cortex as interpreted in the operating room (O.R.) gallery by Herbert Jasper. Localizations of sensory and motor responses were also elicited by Penfield's stimulation. It was customary to mark the points of stimulation and of ECG abnormalities by sterile tickets (of letters or numbers) placed on the exposed cortex together with a white thread delineating the focal area to be excised. These findings were photographed with the gallery camera by Charles Hodge, the MNI's master photographer. In addition, Penfield made sketches and annotated diagrams of the observations. Surely this was history in the making. I personally think that Penfield was frustrated by some skeptical critics or nonbelievers in localization. He never got the full recognition or the surely deserved Nobel prize, but for us participants it was a tremendous experience.

Perhaps the most fascinating aspect was the ability to facilitate the expression of the patient's own seizure pattern. In a parietal lobe focus, stimulation could elicit a bit of music (the patient humming or singing during the stimulus but losing the tune completely when the stimulus was stopped). Others saw the edge of a flag flapping in the breeze or a complex outdoor or indoor scene (perhaps from childhood), and in many cases a sort of extracorporeal perspective of one's self. We who scrubbed in on these cases saw and heard very clearly and without uncertainties. They stick with you unforgetably. Penfield tried to summarize much of his cerebral localization results by diagramming them in the form of an homunculus, e.g., of localizations in the primary motor and sensory strips of the cerebral cortex. Critics unmercifully ridiculed these homunculi. I vividly remember sitting through a lecture at University College, London, at which F. M. R. Walshe engaged in such ridicule. Walshe was an able speaker and had the audience rolling in the aisles with laughter. I was embarrassed and angry. However, Penfield had his revenge. At a 1952 meeting of the Canadian Neurological Society in Banff, Alberta, Canada, both Penfield and Walshe were featured speakers. Walshe gave his usual sarcastic critique. Penfield was not a good speaker, tending to read a carefully crafted exposition. However, Walshe angered him. He literally tore up his talk and launched into a spontaneous defense of his findings

and concepts that utterly demolished Walshe and led us MNI staffers to literally stand up and cheer for Penfield.

On the other hand, Penfield could be difficult. A case in point was a patient with a left-sided subtentorial meningioma. It was a difficult exposure and extirpation, necessitating more than the usual vein ligations. Penfield selected this case for presentation at the traditional Monday morning grand rounds at 3 days postop. Ordinarily, the chief resident would present the case, but the incumbent Francis (Frank) O'Brien was recuperating from a tonsillectomy, so the responsibility devolved on me. As was customary, I gave the patient a thorough neurological examination early that Monday morning. He was doing well, but to my surprise he exhibited a pronounced nominal aphasia. I thought this of interest and highlighted it in my case presentation. I saw Dr. Penfield sweep off his glasses—a sure sign of displeasure—and he stopped me and took over the presentation with the remark that the patient was not aphasic. That placed me in an uncomfortable position, reinforced by a meeting with Penfield in his office after rounds. The implication was that my future at the MNI was in grave difficulty. I sought out Frank O'Brien for advice. He smiled and welcomed me to the select group who had already gone through this kind of experience. Indeed, shortly afterwards Penfield sent for me again and apologized, saying that he had reexamined the patient and confirmed my observation that he was aphasic. I was vindicated; the crisis was over.

At the end of my residency year I faced a decision: to continue the clinical residency program or to return to the research lab. I opted for the latter, so I took on neurochemical research, now headed by Allan Elliott since the untimely demise of Donald McEachern. The course seemed clear: study ACh content and metabolism in the cerebrocortical samples being excised by Penfield at surgery for focal epilepsy. My year scrubbing with the Penfield team would stand me in good stead since I now knew the limitations under which the surgeon operated and the criteria used to characterize the brain samples. It became my habit to sit in the OR gallery to observe the results of cortical stimulation and ECG recordings and to personally pick up the excised cortical samples for immediate processing and study in the lab. It was not always usual for Penfield to excise the brain samples since it was easier to effect removals by subpial suction. He repeatedly wanted to know why I could not use what was essentially a tissue homogenate in the suction bottle. Of course, we wanted a whole piece of tissue with cells and connections relatively intact, but I never fully persuaded Penfield of this desideratum. The principal problem, of course, was the securing of relatively normal cortical samples.

My initial approaches were to assay the content of ACh, the activity of AChE; the responses of slices of the cortical samples during incubation *in*

vitro with respect to content and synthesis of ACh intra- and extracellularly, and the histological appearance of the samples. There were parallel experimental animal studies, essentially on normal brain tissue since there were few, if any, animal seizure preparations comparable to the human patient material. Unlike most traditional biochemists. I eschewed the rat and chose the cat as my principal experimental animal—a choice dictated by brain, and hence sample size, and by the fact that the cat was the choice of neurophysiologists.

The procedures were fairly standard—mostly manometric methods for AChE and for incubations, using Warburg-type vessels and manometers. The assays for ACh were carried out on the dorsal muscle of the leech, as recorded on smoked or ink-pen drums. The leech was a feasible assay preparation because the tissue levels of ACh were sufficient to fall within its assay ranges. I should note that the manometric techniques were a specialty of Allan Elliott, who inculcated all his graduate students with manometric skills, including the ultimate challenge of differential manometry with Summerson (double) manometers and Dixon–Keilin reaction vessels. Elliott had studied at Cambridge with Gowland Hopkins and with both Dixon and Keilin and was probably as proficient with these techniques as anyone in the world. I was ably assisted by Murray Bornstein, a pre-med student at McGill who went on to medical school at Lausanne, Switzerland, and to a distinguished neurological career at Albert Einstein Medical School in the Bronx, New York. We shared the neurochemistry lab with Elliott's students, Marion Birmingham, James Webb, and Hugh McLennan, plus Elliott's technical assistant Nora Henderson. Marion Birmingham went on to a fruitful career at the Allen Memorial Psychiatric Institute at McGill, and Hugh McLennan became professor and chairman of physiology at the University of British Columbia in Vancouver. The lab was located on the seventh floor of the MNI building and just down the hall from the animal quarters, superbly supervised by Mary Roach, R.N., and Charles (Steve) Stevens, primarily for Jasper's neurophysiology labs.

As I began these studies, several unexpected and interesting aspects developed. It was obvious that ACh levels in brain increased and remained high during anesthesia. This phenomenon was carefully studied by Elliott with Roy Swank and Nora Henderson, and later by Jasper and Frank (Hank) MacIntosh in cortical perfusion experiments. Thus, our experimental animals could not be sacrificed by anesthetization for brain sampling but had to be managed by instantaneously lethal decapitation. Furthermore, it developed that the levels (i.e., content) of ACh decreased rapidly after death (excision) according to the decay formula $A = Kt^{-k}$, where A is the total ACh content, K is a constant characteristic of the species, t, is the time after excision/death, and k is a constant equal to about 0.5 for all species. It was possible to adjust ACh levels to a fixed interval after excision, although one is always reluctant to depend on such

manipulations. Finally, it was obvious that the ACh levels/activities in human cortex were significantly lower than in cat cerebral cortex. Further study of this phenomenon in a variety of species from mouse to man demonstrated a comparative phylogenetic regression that related content/activity as a function of species brain weight, according to the formula $A = K_A W^k$, where A is the activity per unit weight of tissue, K_A is a constant characteristic of the component measured, W is the total species brain weight, and k is the regression coefficient for log A vs log W for various species. Again, one is a little uncomfortable with these data since there was no nonhuman species to anchor the human data. Only elephant brain at 4 kg or great whale brains at 6 or 7 kg would serve (Tower and Elliot, 1952a).

We wondered what these findings meant. Could the density and/or size of neurons be specifying the species data? Accordingly, I investigated the cerebrocortical neuron density in the range of species from mouse to elephant and whale. I was greatly helped by Jerzy Olszewski at the MNI, who prepared the Nissl-stained sections from which I enumerated the neurons. The elephant specimens were obtained from the elephant Alice, who died at Luna Park outside New York City. It was through the generosity of Gerhardt Von Bonin that I obtained these sections originally prepared by Fred Mettler at Columbia P & S. Professor Jan Jansen at the University of Oslo, Norway, kindly supplied me with blocks of fin whale (*Balaenoptera physalus*) cerebral cortex (Fig. 2). The result of this neuronal cell density survey indeed illustrated a decrease of cerebrocortical neuronal density as a function of average species brain weight, according to the expression $N = K_N W^k$, where N is neurons per unit volume K_N

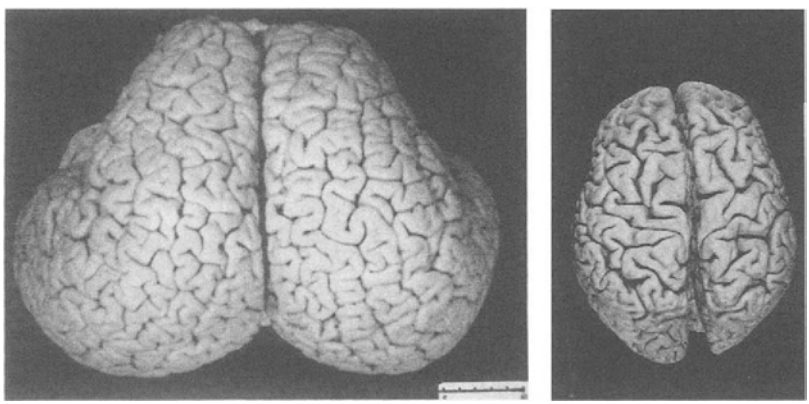


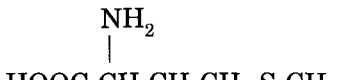
Fig. 2. Photographs of the dorsal aspects of the brain of the adult fin whale, *Balaenoptera physalus* (left) and of normal adult man (right). Both brains were formalin fixed and photographed at the same magnification (scales in centimeters) without dura or pia-arachnoid.

is a constant, W is the species brain weight, and k is the regression coefficient for log N vs log W. Sharif, in Von Bonin's laboratory, found a similar relationship among the primate species from, *Tarsius* to the chimpanzee and man. Von Bonin suggested that I report these data in the *Journal of Comparative Neurology* together with Sharif's paper on primate cerebral cortex (Tower, 1954). It was from these studies that I developed an interest in comparative studies, both phylogenetic and ontogenetic. It surprises me how relatively little attention is paid to these aspects of neurochemical investigations today. What about the original problem relating to epileptogenic foci in human brain? Two findings were evident. First, I was able to confirm Alfred Pope's earlier observation that the AChE activity in epileptogenic cortical foci was significantly elevated above that in "normal" control specimens. My results were obtained by a different (manometric) assay procedure and on a larger sample size. We have assumed that this finding reflected chronically elevated levels of ACh extracellularly in discharging foci—an hypothesis still to be tested.

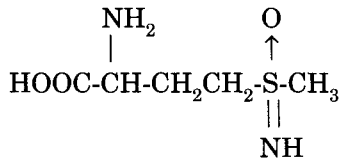
For the incubation studies we cut cortical slices with a Stadie–Riggs microtome at 0.45 mm thickness and used a bicarbonate-buffered Ringer medium (devised by Elliott) containing 27 mM K^+ (as suggested by studies from Hans Krebs) and 95% 0_2–5% CO_2 in the gas phase. Under such conditions the "control" cortical slices, initially depleted of "bound" or tissue ACh, synthesized significant levels of ACh during an hour's incubation—the average increase amounting to 0.5 μg of ACh/g of tissue (range 0.5–0.85). In contrast, the focal epileptogenic slices failed to increase tissue levels at all, averaging at 1-hr incubation 0.0 (range –0.1 to 0.25 μg. ACh for 11 specimens). What we dealt with was then called bound acetylcholine (a tissue fraction released only after weak acidification). This was, of course, before we knew about the synaptic vesicles that package neurotransmitters and all the factors involved in synthesis, storage, release, and reception at the postsynaptic site. We interpreted this finding as a defect in the "binding" process or increased lability of "release" mechanisms (Tower and Elliot, 1952b). Subsequent studies by others tended to confirm our findings, but a later attempt by Hanna Pappius in Elliott's lab failed to reproduce our results. I was not immediately apprised of Pappius' results and in any case was not in a position to readdress the problem. I was by then at the NIH, I had no source of human material (Baldwin having terminated his project), and we still lacked a good chemical procedure for determining ACh. I have every confidence in my original data, especially in view of several circumstantial consistencies, and I am puzzled by the generally low values obtained by Pappius, regardless of specimen type—factors such as failure to remove the pia-arachnoid before slicing, uncertainties over the precise nature of the cortical sample and insensitivities occasionally encountered

in leech assays. Nevertheless, one is left with results that are not clear-cut. Increased lability of tissue stores of ACh and elevated extraceullular levels of ACh remain working hypotheses in search of better experimental conditions.

In view of the difficulties inherent in the human studies, we sought experimental animal preparations. At that time flour millers altered their method for treating flour to rid it of weevils by resorting to treatment with nitrogen trichloride (agene: NCl_3) to produce so-called agenized flour. Dogs fed dog biscuits made with such flour developed chronic, recurrent generalized seizures. We reproduced this syndrome but were spared the cumbersome preparations by the discovery by L. F. Reiner (at Wallace & Tiernan Products, Inc.) of the toxic agent in agenized flour, namely, methionine sulfoximine (MSO), a most potent convulsant causing semichronic generalized seizures in a variety of species including the cat:



Methionine



Methionine sulfoximine

Therefore, we had available an animal model for study (Tower, 1958a). We reproduced in cat cerebral cortex the findings previously obtained in the human specimens. A feature of these studies was the ability to correct or reverse the defect in ACh binding by adding certain amino acids (L-methionine or L-glutamic acid) to the incubating slices. These experiments led to subsequent studies on glutamate and glutamine in incubated cerebrocortical slices. Suffice it to say here that Edmund Peters and I showed that a key abnormality in cats with seizures induced by MSO was inhibition of glutamine synthesis by incubated cerebrocortical slices (Peters and Tower, 1959). Those studies done at the NIH led to enzymological investigations by Alton Meister (then also at the NIH), who showed the abnormality to be in the enzyme glutamine synthase.

During the years 1949–1951, several events occurred that warrant attention. First, my studies on ACh metabolism in human epileptogenic foci were accepted as my doctoral thesis for a Ph.D. in experimental neurology, conferred by McGill University in July 1951. I had to pass two language exams (French and German—the latter a passage about the physiology of the dormouse). My outside examiners on my thesis were two biochemists, Roger Rossiter (University of Western Ontario) and Heinrich Waelsch (Columbia P & S), both of whom became close friends subsequently. At the time, the John and Mary R.

Markle Foundation established a program of 5-year, $30,000 awards as Markle Scholars in Medical Sciences. Candidates were selected and nominated, one per medical school, with final selections made by a panel of prominent scholars after individual interviews with the candidates. In 1950 I was nominated by McGill and met for 3 days with the Canadian selection panel at the posh Seigneury Club (located between Ottawa and Montreal). I was honored by selection as one of the Canadian scholars beginning in 1951. At this time I was also appointed associate neurochemist at the MNI and assistant professor of experimental neurology on the McGill Faculty of Medicine. For the first half of 1951 I was awarded an externeship in neurology at the famous London neurological hospital at Queen Square, with assignment to E. Arnold Carmichael's "firm." It was a marvelous experience to see most of the neurological spectrum and to learn from famous teachers: Carmichael, Godwin Greenfield, Dennis Williams, Charles Symonds, Wylie McKissock, and more. While in England I was able to meet with Sir Edward Mellanby (who studied the effects of agenized flour), Sir Henry Dale (the "father" of ACh) and some of his associates (Wilhelm Feldberg, Catharine Hebb, *et al.*), and J. Z. Young (then studying memory in the octopus). Through my wife's sister Avis and her Norwegian husband Karl Karlsen (in the Nova Scotia whaling and fishing business), I was able to travel to Norway, Oslo, and Brandal (outside Ålesund) to meet Karl's family and to learn about the herring fisheries and whale catching.

At the time, Montreal was an active center of research on acetylcholine—at the MNI with Elliott's biochemical group, and Jasper's physiological group; at the Montreal General Hospital's Research Institute directed by Judah Quastel and located just a block down the street, and across the street in the Department of Physiology in the NcGill Faculty of Medicine with Frank C. (Hank) MacIntosh as chairman and Arnold Burgin (later Sir Arnold). Hank MacIntosh invited John Eccles (later Sir John) to lecture at McGill in (I think) 1950. All of us were invited to attend. It was a memorable occasion. We had all read the series of publications from Eccles' lab in Australia, a series of electrophysiological studies that led Eccles to conclude that neuromuscular transmission could *not* be chemically mediated but was a strictly electrically mediated process. At his McGill lecture, to our great surprise, Eccles completely reversed himself by stating that neuromuscular transmission must be chemically mediated with ACh as the transmitter agent. We were witnessing history in the making even before his next publication. Incidentally, friendship with Jack Eccles grew out of that meeting.

Later, another event touched all of us in the neurochemistry lab. Ernst Florey arrived, bringing his studies on factor I, an inhibitory substance active on the crayfish stretch receptor. Stephen Kuffler and colleagues at

Harvard were also studying this preparation. Also Eugene Roberts in St. Louis had found a new amino acid, when he paper chromatographed brain tissue extracts, that he identified as γ-aminobutyric acid (GABA). Roberts got credit for the discovery and much of the biochemistry. However, Florey and colleagues at the MNI (Elliott, Jasper, McLennan, and Bazemore) got credit for recognizing its role in inhibition in the central nervous system. Florey and Elliott lacked the chromatographic expertise to isolate and identify factor I; they called upon Al Bazemore from Merck & Co. in Rahway, New Jersey, who set up the chromatographic apparatus that permitted isolation of factor I in pure form and its identification as GABA. Thus, the mammalian central nervous system acquired its first inhibitory transmitter.

One more event wrought major changes in my career. The Korean War broke and forces within the United State were mobilized. In 1953, the U.S. Navy asserted its need to have me satisfy the rest of my draft obligation (from World War II). I explored possible alternatives to going to Korea but it began to look very much as if I would join William Caveness in a head injury–epilepsy project aboard ship off the coast of Korea. Then came an invitation from Milton Shy and Maitland Baldwin (late of the MNI and by then in Denver) to join them in inaugurating a neurological and neurosurgical clinical research program at the newly authorized National Institute of Neurological Diseases and Blindness (NINDB) at the NIH in Bethesda. I responded that I would like to accept their invitation if they could so persuade the U.S. Navy. Enter the new director of the NINDB Pearce Bailey, an old hand at such political problems. I know not how, but Pearce got me out of the navy and appointed to active duty with the commissioned corps of the U.S. Public Health Service, which essentially staffed and ran the NIH. A few others who heard about my switch tried to duplicate it but the navy would not repeat. Basically, I still had to satisfy my residual military obligation but could do so in a research position at the NIH rather than overseas. Therefore my family moved to the Bethesda–Chevy Chase area of the Maryland suburbs of Washington, DC, and I entered on active duty at the NIH on July 11, 1953. My assignment was to create and head a section of clinical neurochemistry under the clinical directorship of Milton Shy and to embark on a research program comparable to that which I was leaving in Montreal. At the end of my 2 years of obligated uniformed service, it was my original intention to return to the MNI, where Penfield had promised me a permanent position. That did not happen, as I soon cast my lot with the NINDB and the NIH for the rest of my active research career. However Montreal and the MNI hold many fond memories, especially of my fellow staff members: besides Penfield, Elliott, Jasper, and Elvidge, there were William Cone (neurosurgeon par excellence and neuropathologist), Francis NcNaughton and Preston Robb (both fine neurologists), Donald McCrae (neuroradiologist),

Brenda Milner (neuropsychology), a company of expert and dedicated nurses under Eileen Flanigan, and my many associated fellows and residents. The $6\frac{1}{2}$ years there are irreplaceable.

At the National Institutes of Health (NIH): NINDB and NINDS.

By 1953 the NIH in Bethesda, MD consisted of 10 research institutes and had just brought on line its 13-story Clinical Center building consisting of 550 beds and more than 1000 contiguous research laboratories. The Neurology Institute (NINDB) had been authorized by the U.S. Congress in 1951, with Pearce Bailey as director. With the opening of the new Clinical Center, the clinical research program of the NINDB was inaugurated. Its staffing was primarily by MNI "alumni"; in fact, it was the largest collection of MNI trainees anywhere except in Montreal. The original group included Milton Shy (clinical director and neurologist), Maitland Baldwin (neurosurgeon), Choh-luh Li (neurophysiology, microelectrodes), Cosimo Ajmone-Marsan (EEG and neurophysiology), Igor Klatzo (neuropathology), Anatole Dekaban (pediatric neurology), John Van Buren (neurosurgeon, neuroanatomist), John Lord (consulting neurosurgeon), Shirley Lewis (OR Nurse), and myself (neurochemist). Additional staff included Paul Chatfield (neurophysiology), Ellsworth (Buster) Alvord (neuropathology), Giovanni DiChiro (neuroradiology), Richard Irwin (neuropharmacology), Laurence Frost (neuropsychology), and in ophthalmology William Hart, then Ludwig Von Sallmann. Our basic science or nonclinical research labs were combined with those of the National Institute of Mental Health (NIMH) under the direction of Seymour Kety. The NINDB share included Kenneth (K. C.) Cole (biophysics, voltage clamp), Karl Frank (spinal cord physiology in Wade Marshall's lab) William Windle (neuroanatomy), Jan Cammermeyer (neuropathology), and Roscoe Brady (lipid neurochemistry). It was a reasonably impressive and talented group that lost little time in initiating active contributory research.

One of the great features of the NIH has been the diversity and breadth of talents available on the Bethesda campus. It was this attribute that changed my thinking from an eventual planned return to the MNI to a decision to stay at the NIH. A case in point was my need to generate more reagent for my assays of glutamic acid and glutamine. The microdistillation and manometric assays that I used depended on a protease preparation from cultures of *Clostridium perfringens* (the gas gangrene bacillus). The protease specifically deamidated free glutamine [$GluNH_2 \rightarrow Glu + NH_3$] so that the released amide ammonia could be microdistilled and determined colorimetrically. Furthermore, the protease specifically decarboxylated total free glutamic acid [$Glu + GluNH_2$], with the liberated CO_2

determined manometrically. With another appropriate protease treatment the protein-bound Glu and $GluNH_2$ could be assayed as well. The preparation of the *C1. perfringens* enzymes involved large-scale (carboy) cultures, harvesting the bacterial cells with a continuous centrifuge, and lyophilizing (freeze-drying) the harvest. A Sharpless cream-separator continuous centrifuge filled the bill, but not everyone has such an instrument; at the NIH I found an old friend, Chris Anfinsen, who was able to fill my needs and arm me with several years' worth of enzyme preparations. Shortly I was able to return the favor. Chris was working in the arthritis institute (NIAMD) on the amino acid sequence and structure of the protein ribonuclease. Anfinsen came to me with a problem I could address. In the amino acid sequence of the decapeptide, residues11–20 of the RNase S-peptide, there were an Asp (aspartic acid) and a Glu and an amide. Was it $AspNH_2$ at residue 14 or $GluNH_2$ at residue 11? Standard techniques of acid hydrolysis deamidated the residues, but my Viokase protease released protein-bound amino acids with their amide groups still intact. Thus, I was able to tell Anfinsen that the 11–20 decapeptide contained a glutamine ($GluNH_2$) residue at position 11. This finding allowed Anfinsen to complete the amino acid sequence for ribonuclease. We published simultanous papers in the *Journal of Biological Chemistry* (Tower *et al*, 1962). Chris was awarded the Nobel prize in chemistry for his work. My contribution was small, but it was nice to get that close to a Nobel.

Early on in the research at NINDB–NIH I acquired several important new techniques. One was the use of single- and two-dimensional paper chromatographic techniques for separation, identification, and quantification of components in mixtures of amino acids, sugars, and the like. Another was the acquisition of abilities to handle and analyze radioisotope tracers. For these latter techniques Milton Shy and I enrolled in a 3-week course in radioisotope techniques at the Oak Ridge Institute of Nuclear Studies (Oak Ridge, TN), adjacent to the AEC nuclear reactor facilities there. Hands-on teaching was provided by William Pollard and staff. Passing this course armed us with a certificate that entitled us to procure and use radioisotopes in our own research.

Even though Mait Baldwin had been trained by Penfield in the evaluation and surgical excision of epileptogenic cerebrocortical foci, and even though Baldwin initiated such a program at the NIH, the numbers of suitable patients had decreased and the NINDB program was slow to be established. Thus, my studies increasingly turned to experimental animal work, especially on glutamate and on K^+, Na^+, and brain swelling, and to clinical applications, notably trials of asparagine and of GABA as anticonvulsants and highlighting major abnormalities from two patients, from whom we obtained both a "normal" and an epileptogenic temporal lobe sample to illustrate the point:

Patient G.L., ♀, age 29: left temporal (Sylvian) focus

	Acetylcholinesterase (μmol/g/hr)	"Bound" acetylcholine (mμmol/g)	
Cortical slices		Initial	1-hr incubation
"Normal"	47	8.55	11.8
Epileptogenic focus	85	6.5	6.4

Patient C.G., ♂ age 29: right temporal (Sylvian) focus

	Glutamic acid (μmol/g)		Glutamine (μmol/g)	
Cortical slices	Initial	1-hr incububation.	Initial	1-hr incubation.
"Normal"	7.35	10.35	2.2	3.75
Epileptogenic focus	7.35	6.0	2.85	4.2

These examples are representative of observations on totals of four "normal" and 18 epileptogenic patient samples for acetylcholine studies and for 4 normal and 11 epileptogenic patient samples for glutamate studies (p101; 172; Tower, 1958b).In each set of studies reversals of the respective defects occurred with the *in vitro* addition of L-asparagine (10 mmolar) during incubation while not affecting the levels in normal slices. Histological examinations did not reveal obvious differences.

At that time, glutamic acid had been identified as one of the few amino acids capable of supporting oxygen utilization by brain tissue. Studies reported by Quastel, by Krebs, and by Weil-Malherbe so attested. At the same time there were reports of the amelioration of methionine sulfoximine toxicity in microorganisms by incubation with glutamate or methionine. In retrospect, these clues might seem a bit tenuous but we were persuaded to embark on analogous trials in cerebrocortical slices from MSO cats or human epileptogenic foci by incubating them with added glutamine, asparagine, and methionine, and eventually to embark on clinical trials in seizure patients. Subsequently, we have learned from Richard Olsen and others that glutamate is an excitatory transmitter at a variety of postsynaptic receptors; from Quastel and from Carl Cotman, Gary Lynch, and colleagues that after a glutamatergic neuron releases transmitter Glu upon stimulation, it is inactivated by uptake into adjacent astrocytes and amidation to glutamine, which then shifts to the neuronal presynaptic ending to be deamidated to transmitter Glu, ready for the next stimulus; from Michael Norenberg and coworkers that in brain glutamine synthetase is uniquely astrocytic in location; from Eugene Roberts

and from Ernst Florey that GABA (derived by decarboxylation of Glu) is a principal inhibitory transmitter; and from Heinrich Waelsch and colleagues that glutamate metabolism is compartmented into at least two metabolic cycles that respond differently to seizure conditions. It is this sequence of events that is blocked by the inhibition of glutamine synthetase by methionine sulfoximine [as Ed Peters and I (1959) had originally shown]. Alton Meister and coworkers have demonstrated the inhibition to be irreversible, due to the phosphorylation of the sulfoximine nitrogen (and cleavage of ATP to ADP) with tight binding of the MSO-phosphate and the ADP to the enzyme (Ronzio *et al.* 1969). As Waelsch has pointed out, the brain contains no urea-synthesizing capacity so that glutamine synthetase is essentially the sole mechanism for the brain to deal with excess ammonia. Thus, it is not surprising that Norenberg observed in animals with MSO-induced seizures a significant development of Alzheimer type II astrocytes comparable to the abnormalities seen in hepatic encephalopathies or in hyperammonemia.

Again in retrospect, our resort to clinical trials with asparagine, glutamine, or GABA against seizures might be considered a bit premature. Nonetheless, we set about a small clinical study at the NIH and at four other clinics (Charlottesville, VA, under Walter Klingman; Chapel Hill, NC, under Thomas Farmer; Buffalo, NY, under Bernard Smith; and Baltimore, MD, under Charles Van Buskirk). Altogether, about 300 seizure patients participated in the study for as long as 6 months. The logistics involved preparation of lyophilized sterile samples of L-glutamine and of L-asparagine The latter was no problem to formulate, but the glutamine required special handling because of the lability of its amide nitrogen. Initial preparations were produced for us by Ayerst, McKenna & Harrison, Ltd., in Montreal, and subsequent preparations for intravenous use were prepared by the research division of Merck & Co., Inc. (Rahway, NJ), under Lewis Sarett (director) and an old friend Joseph Hawkins (principal investigator). Merck prepared sterile, lyophilized L-asparagine and specially filtered, sterile L-glutamine for clinical intravenous use. Six seizure patients were tried on the i.v. preparations at a dose of 1.0 mmol/kg body weight—four received several repeated doses—all well tolerated but with variable effects on their EEGs. Altogether, we, at the NIH, placed 9 seizure patients on pure oral L-asparagine (purchased commercially) at a dose of 2 mmol (136 mg)/kg body weight, four times daily. The asparagine was most conveniently dissolved in fruit juice or chocolate milk for ingestion. We followed our patients for many months and observed significant improvement (clinical and EEG) in the majority. Data from the other four clinics participating in the study indicated improved seizure control in about 40% of the patients. In principle, we had a reasonably promising anticonvulsant in L-asparagine, but the material was too bulky, too inconvenient to formulate,

and too costly per dose so that it could not have competed successfully with existing anticonvulsants.

In addition, we initiated clinical trials with oral GABA, prepared for us by the Merck group. They also synthesized the cyclic form of GABA, 2-pyrrolidinone (Hawkins and Sarett, 1957), which proved to be a source for GABA after *in vivo* administration. The Merck group carried out extensive tests on GABA for acute and chronic toxicity. No toxicity or untoward effects were observed in their rats and dogs, although several investigators have observed, upon i,v. administration, marked arterial hypotension (a 50% or greater decrease) and hyperventilation. Similar reactions were observed in human volunteers and upon oral administration of 1 or 2 mmol/kg body weight rapid flushing together with paresthesias and malaise commonly occurred. Some tolerance developed and in no case was it necessary to terminate the trials. Altogether, 14 human seizure patients were studied, 11 of which were followed for periods of 3 months to 2 years on oral doses of GABA of 2 mmol/kg body weight four times daily. Four cases achieved significant improvement in seizure control; in one the control was complete (Fig. 3): J.D., a 14-year-old girl with petit mal seizures, was observed for 7 months while on trimethadione and phenytoin medication, with a monthly average of 402 (±68) seizures per month. When

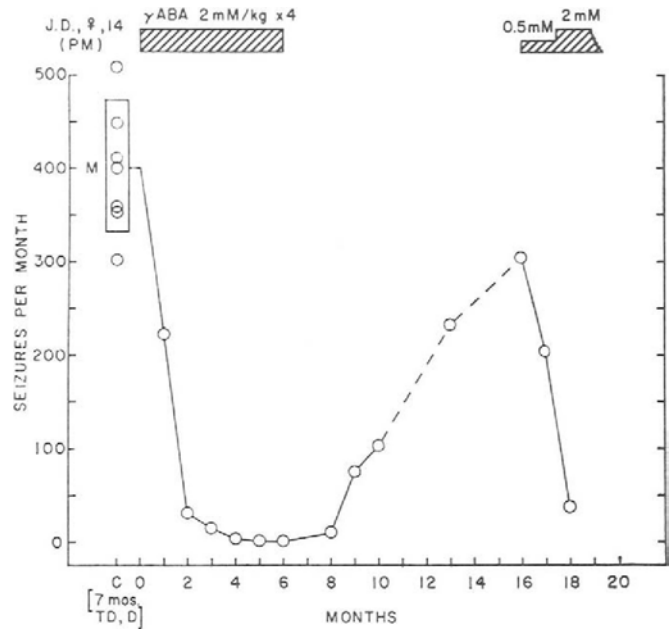


Fig. 3. Monthly seizure record of patient J.D. Petit mal seizure frequency for the 7-month control period (C), while treated with trimethadione and phenytoin, had a mean value (*M*) of 402 (± 68).

switched to GABA, there was a dramatic and complete decline in petit mal seizure frequency to zero within 2 months and this was sustained for 4 months. At that point the GABA was stopped; her petit mal seizures rapidly recurred at a rate of at least 5–10 daily but again decreased to near zero upon resumption of the same GABA dosage. The paroxysmal high-voltage epilepti form activity in this patient's EEG completely disappeared upon the oral GABA treatment (Tower, 1960a).

Several other aspects of our GABA studies deserve brief mention. We wondered about the role of GABA in intermediary (citric acid cycle) metabolism because the GABA pathway (Glu $\rightarrow$(1) GABA + CO_2 $\rightarrow$(2) succinate) provides an alternate to the oxidative decarboxylation step: α-ketoglutarate $\rightarrow$ succinate. Moreover, the decarboxylase and transaminase steps (reactions 1 and 2) in the GABA pathway both require pyridoxine (vitamin B_6) in the form of pyridoxal phosphate as coenzyme. Deficiencies of B_6 are commonly associated with seizures. In fact, there is a genetically based disorder—pyridoxine dependency—that is characterized by neonatal (or even pre-natal) generalized seizures controllable only with sizable doses of pyridoxine. If treatment is delayed beyond birth, mental retardation supervenes and is not reversible. It presumably reflects the markedly delayed central nervous system (CNS) myelination in untreated patients. To date, 24 cases (of a total of 41 siblings) from 12 families have been reported (Tower, 1969). We shall probably never know the full story because now all pediatricians routinely administer B_6 to any newborn with seizures. Swedish investigators under Johansson suggested that there is an abnormality of the relevant Glu-decarboxylase apoenzyme which only binds the coenzyme pyridoxal phosphate loosely; hence the need for an increased B_6 intake to keep the apoenzyme saturated (Gentz *et al.*, 1967).

We were able to restudy Patient A.N. (female, age 7 years), the original case of pyridoxine dependency who had been maintained seizure free since age of 2 years on 10 mg of pyridoxine orally per day. Nevertheless, she exhibited severe mental retardation. In our study we interrupted B_6 therapy; after 72 hr clinical seizures and epileptiform activity in her EEG were manifest. These seizures and symptoms were abolished within 2 min after 15 mg of pyridoxine was administered intravenously. We repeated this sequence of events with the addition of measurements of cerebral blood flow, cerebral oxygen consumption, and respiratory quotient—these latter procedures were carried out by Nils Lassen and Louis Sokoloff. During the seizure, cerebral blood flow, O_2 consumption, A-V difference of O_2, and (RQ) respiratory quotient were all markedly depressed below expected normal values for children of this age. After termination of the seizure by i.v. B_6, there was a slight rise in cerebral blood flow (from 63 to 70 ml/100 g/min), a moderate increase in $CMRO_2$ (from 3.3 to 4.4 ml O_2/100 g/min; $\cong$ 0.05), and restoration of A-V O_2 difference and RQ to normal (5.26–6.23 and 0.85–0.96, respectively). Additional studies seemed

to be precluded by the extreme rarity of pyridoxine dependency (Sokoloff *et al.*, 1959). The observations seemed to favor a role for GABA metabolism in oxidative metabolism, in addition to its role as an inhibitory transmitter. Indeed, J. Marie and colleagues at the Hôpital des Enfants Malades in Paris reported subsequently on another pyridoxine-dependent patient, to whom they administered GABA intravenously to correct the depressed cerebral oxygen consumption (Marie *et al.*, 1961).

In parallel we collaborated with Olaf Mickelsen at the NIH to produce B_6-deficient kittens whose cerebrocortical slices exhibited significant depression of O_2 consumption (down to 66 % of normal controls), correctable by addition of pyridoxal phosphate or of GABA *in vitro*. Our experiments indicated that *in vitro* as much as 40 % of substrate being metabolized through the stage from α-ketoglutarate to succinate proceeded via glutamic decarboxylase and GABA. Data *in vivo* suggested that the percentage metabolized by the GABA "shunt" might be closer to 10–20 %, but even so a potentially significant role for GABA in oxidative metabolism was suggested (McKhann and Tower, 1959, 1961a; McKhann *et al.*, 1960). One should not overlook the toxic effects of ammonia in such preparations, and indeed Guy McKhann and I called attention to a possible direct interference by ammonia on the oxidative decarboxylation of pyruvate and of α-ketoglutarate (McKhann and Tower, 1961b). Later in correspondence with Sir Rudolph Peters (at Oxford), he wrote that he believed in the correctness of our observations. The matter is still moot.

About this time I was approached by the publisher Charles C Thomas, which was sponsoring a series of books titled *Lectures in Living Chemistry*. Would I do a volume on the neurochemistry of seizures? This seemed like a good project to summarize what I knew or thought I knew at that point. There were no royalties, but the book (published in 1960) proved quite popular over the next few years. It was even translated into Japanese and published in Osaka in 1964 (Tower, 1960b, 1964). The translation was prepared and published without my knowledge and, since I do not read Japanese, I have no idea of the quality of the translation. There were no Japanese royalties either.

The last major area of research that we tackled involved cerebral fluids and electrolytes. We already knew about the observations by Henry McIlwain (London), on leakage and reuptake of K^+ in incubated cerebrocortical slices and observations by Arthur Ward (Seattle) and David Prince (Stanford) and others on the role of K^+ in seizures. At this time, we were also confronted with a controversy over extracellular spaces in brain, notably the contention by some electron microscopers that there was no extracellular fluid space(s) in central nervous tissue. We neurochemists could not believe that this was true. Both McIlwain and I had much evidence to the contrary. I turned to my colleague Theodor Wanko, an NINDB electron microscopist, for a specific study of the problems of neural

tissue fixation. With unbuffered fixatives the brain tissue sections took up extra fluid, swelling by as much as 50%, and then shrank during dehydration to one-half or one-third the size of the original sample. What distortions in architecture were introduced? Wanko found that very short fixation times (as little as 1 min) with buffered fixatives provided excellent fixation with osmium. Our incubated slices of cerebral cortex looked much more like biopsy samples, and there clearly were extracellular spaces in our sections. (Wanko and Tower, 1964).

Robert Bourke in my laboratory subsequently carried out extensive studies on cerebral fluids and electrolytes. He found significant differences in the size *in vivo* of fluid spaces in the cerebral cortex of nine mammalian species, as measured by chloride (Cl^-), ^{14}C-thiocyanate, ^{14}C-sucrose, and ^{14}C-inulin injected intracisternally. After suitable equilibration, subarachnoid CSF and the subadjacent cerebral cortex were sampled in mice, rats, guinea pigs, rabbits, cats, *Macaca multta* monkeys, sheep, chimpanzees, and beef cattle. There was insufficient CSF in the small rodents (mice and rats) to do more than electrolyte analyses. From smaller to larger species the measured fluid spaces exhibited parallel, significant increases, varying as a function of the logarithm of the average species brain weight: For example, for sucrose or inulin cortical spaces— guinea pig, 20.8%, cat, 27.4%, and chimpanzee, 30.4% (Bourke *et al.*, 1965). I am not aware that such a comparative or phylogenetic correlation had been previously appreciated, and today it is generally ignored, although we have been able to extend some of the data to include fin and sperm whale (Tower and Young, 1973).

Further studies centered upon *in vitro* observations on cat brain and other tissues to sort out the complexities of fluids and electrolytes in such preparations. We took special cognizance of previous work on rat and guinea pig cerebral cortex by Hanna Pappius and Allan Elliott in Montreal and by Sylvio Varon and Henry McIlwain in London. The outcome of a very laborious and extensive series of experiments was the delineation of 3 major types of swelling, or increase in fluid uptake, by cat cerebrocortical slices: (*i*) adherent fluid from the incubation medium, amounting to 5–10% of the initial fresh weight of the tissue slice and accessible to both inulin and chloride; (*ii*) "preparatory" swelling of the tissue slices that occurs during the gassing of incubation flasks (with 95% O_2–5% CO_2) at room temperature (22°C)—after 5 min the extra fluid totals 15%, accessible to Cl^- but not to inulin, and if the preparatory period takes longer (up to 30 min) the fluid uptake or swelling may reach 50% of the initial fresh weight of the tissue slice; and (*iii*) if the K^+ concentration in the incubation medium is elevated above the usual 5 m*M* level, a third type of swelling or fluid uptake occurs that is a function of both the external K^+ concentration and the presence and external concentration of Cl^- (Tower, 1972). If Cl^- is replaced by isethionate (2-hydroxyethanesulfonate), essentially no

K^+-dependent slice swelling occurs. These observations are symptomatic of the K^+-dependent transport of Cl^- into astrocytes (Gill *et al.*, 1974). There is a natural "experiment" that illustrates this point. By following the fluids and electrolytes of kitten cerebral cortex from 1.5 postnatal days of age until age 120 days, one distinguishes the role of the astrocyte in this context. At birth the incubated cortical slices do not swell and their Cl^- spaces are similar to sucrose and inulin spaces. In other words, these neonatal slices do not behave like adult slices in this respect. At 1 month postnatal age, the cortical slices begin to exhibit during incubation a K^+-dependent swelling (averaging 12.3% of the initial fresh weight of the slices), without any change in Cl^- or sucrose spaces. Little further change is seen until about 3 months postnatal age, with final proliferation of dendrites and myelination of cortical axons to about 50% completion already having taken place. At this time, slice swelling in 27 m*M* K^+ medium is double the amount at age 1 month and the Cl^- space has significantly increased. The late appearance of these characteristics occurs after neuronal maturation and axonal myelination are essentially complete. Only one facet of cerebrocortical maturation is still significantly in progress—proliferation of glial cells (probably astrocytes) (Tower and Bourke, 1966). Thus, it seemed likely that the K^+-dependent slice swelling and the K^+-dependent uptake of Cl^- were manifestations of the saturable transport system in astrocytes, subsequently demonstrated by us (Gill *et al.*, 1974).

The foregoing summaries make the point for the complexities of such research. Not surprisingly we still do not have adequate studies on human cerebrocortical slices, especially from epileptogenic foci. I did succeed in studying four sets of normal and four sets of epileptogenic slices from human patients to give us a hint of what to expect. The normal slices initially contained 72.2 (±3.8) μequiv of K^+ per gram of fresh tissue and during 1-hr of incubation took up 28 μequiv/g to equal cortical biopsy levels at 100.2 (±9.4) μequiv of K^+/g. In contrast, the epileptogenic slices failed to regain the K^+ initially lost: initial K^+ was 72.3 (±6.1) and after 1-hr incubation 80.6 (±2.5) μequiv/g). From the extensive animal experiments carried out by McIlwain and colleagues, using a specially designed incubation apparatus fitted with stimulating microelectrodes, there is no longer any doubt that incubated cerebrocortical slices can be manipulated to discharge and lose K^+, which can then be taken up to restore normal ionic levels and concentrations. The experiments by Li and McIlwain while McIlwain was visiting my lab illustrate the point quite nicely (Fig. 4). Despite the need for more work, I think it justifiable to include the initial loss of K^+ and the failure of its reuptake into incubating cerebrocortical tissue as an element in the complex of neurochemical lesions in human epilepsy. Nevertheless, I am surprised to find in the latest edition of *Jasper's Basic Mechanisms of the Epilepsies* (Delgado-Escueta *et al.*, 1999)

Fig. 4. Injury discharge recorded with a microelectrode from a neuron in a slice of guinea pig cerebral cortex during incubation *in vitro*. The initial discharge was accompanied by a steady potential of –61 mV, and the spike potential measured 97 mV. [unpublished record provided by Dr. Choh-luh Li, obtained during the study reported by Li and McIlwain (*J Physiol* 1957;139:178)].

on p. 35 credit from the editors for "the Tower Hypothesis of a defect in $(K^+)_0$ regulation in human partial epilepsies." I can take no credit for such an hypothesis, especially for partial epilepsies, and I would submit in view of the foregoing discussions that the data do not yet permit such an hypothesis. However, the kind thoughts are appreciated.

A few forays into other areas deserve brief mention. With John Wherrett (now in Toronto) we examined an old problem posed originally by Weil-Malherbe. He noted that under unfavorable conditions the brain released much ammonia and speculated that it might be derived from the amide groups in cerebral proteins. Moreover, Heinrich Waelsch put forth the possibility that protein-bound glutamate and aspartate groups might be amidated or deamidated to nullify or create charges on the proteins (–COOH vs $-CONH_2$), perhaps via such enzymes as transglutaminase. Since we had the Viokase procedure, which would hydrolyze the proteins while maintaining the amidated amino acids intact, we could examine such questions. In incubated cerebrocortical slices there was a fraction of protein-bound glutamine that released ammonia under virtually any manipulation, a release amounting to 16% of the glutaminyl residues of cerebrocortical proteins, thus confirming the original hypothesis of Weil-Malherbe. These labile protein-bound amide groups seem to be peculiar to the cerebrocortical proteins. However, reamidation of the resulting glutamyl residues could not be demonstrated, so we were unable to address Waelsch's proposal. We did find acidic proteins in the microsomal preparations from various tissues, including liver and cerebral cortex, especially in the deoxycholate-soluble ("membrane") subfraction. These acidic proteins were chraracterized by more glutamyl and aspartyl residues without increases in amides (Wherrett and Tower, 1971; Tower and Wherrett, 1971). Further studies by George Allen in my lab led to isolation of a microsomal membrane protein composed primarily of glutamyl (14.5%), aspartyl (16.5%) and lysyl (9.95%) residues (accounting

for 40% of the total residues)(Allen and Tower, 1972). This would be the type of protein that would presumably be required for Waelsch's hypothesis. Note that with our small field-size mass spectrometer, our ^{15}N analyses in these studies were at the borderline of sensitivity. We thought we had evidence of ^{15}N reamidation of the cerebrocortical protein-bound glutamyl residues, but Waelsch could not verify our data using a much larger and more sensitive instrument. Therefore, we did what was called for in a disagreement; we exchanged samples and at the NIH we resorted to the large, sensitive mass spectrometer at the NIH–NIAMD (Wherrett and Tower, 1971), and thus concurred with Waelsch's data.

About this time, the opportunity presented for extending previous observations on samples of whale brain. The Karlsen whaling station in New Harbour, Nova Scotia, was processing several great whales per month. Therefore, I sought to go out on one of the whale catchers to try to obtain a sample of fresh cerebral cortex for various analyses. We devised a compressed-air-driven trochar to sample the brain at sea. To my dismay this proved not to be feasible because I had not allowed for the differences in rise and fall of the ship and of the 60 to 70-foot fin whale floating alongside. A platform mounted on the whale's head would have been necessary in order to utilize the trochar. Therefore, we settled for the haul out at the shore station, where the Canadian government scientist (from the Deptartment of Fisheries) opened the skull for us (with a chain saw:) and delivered to us the huge 7-kg brain. We took perhaps 500 g and, lacking the requisite quick-freezing facilities, we wrapped the sample in aluminum foil and stored it on dry ice. I had a Federal permit to import the whale brain into the United States, but it still caused quite a stir when we went through the border customs station. Back at the NIH our first concern was postmortem autolysis. Electron microscopy (by Milton Brightman) and analyses of myelin basic protein (by Marian Kies) reassured us that very little autolysis had occurred beyond what would be expected in a human brain 1 hr after death. As it turned out, our procedure of taking a large chunk of brain and letting it freeze slowly in the dry ice chest minimized ice crystal formation. Slow thawing also helped. Studies on other brains (e.g., beef brain) confirmed these impressions. When we did our original comparative studies already discussed, we had no anchor point on the plots for brains larger than human brains. Now we found for cortical oxygen consumption that frozen–thawed brain respires at almost exactly 50% of the rate for fresh brains, and the whale brain values fell precisely on the regression curve, thus indirectly anchoring the original curve. We did analogous studies for cortical acetylcholinesterase activity and for cortical Cl^- space (Tower, 1973). In addition, we evaluated the glia–neuron index in the cerebral cortex of various mammalian species and investigated the role of cortical glia (astrocytes primarily), again using the samples of whale brain to provide anchor values for the very large

brains. Double-logarithmic plots of cortical neuron density and of glia–neuron index as functions of species brain weight yielded curves with nearly identical slopes of opposite orientation, which implies that the density of glial cells (astrocytes) in cerebral cortex is essentially constant over the range of species from mouse to great whales (Tower, 1973). The activities of two exclusively glial enzymes, butyrylcholinesterase (BuChE) and carbonic anhydrase, proved to be essentially constant over the range of species studied, providing further evidence for a relative constancy of cortical glial cell density regardless of species. Earlier, Elliott and Henderson had reported data suggesting that anaerobic glycolysis in mammalian cerebral cortex might share a similar relationship. We repeated their study on more species, including whale cerebral cortex homogenates. The relative constancy of the rates of anaerobic glycolysis in cortical samples from mouse to whale strongly implies that this facet of cerebrocortical metabolism is primarily glial (astrocytic ?) in localization (Tower, 1973). I reiterate the value of our access to samples of great whale brains and the many correlations provided by them.

One other investigation deserves brief mention. In the mid-1950s several groups of investigators reported on the effects of 2-deoxy-D-glucose (2-DG) as an inhibitor of glucose metabolism. In effect 2-DG produced a state of simultaneous hyperglycemia and cytoglycopenia, attributable to the fact that 2-DG is phosphorylated by hexokinase but is not metabolized further (posing a block in the step that normally converts glucose 6-phosphate to fructose 6-phosphate). We confirmed and extended *in vitro* the *in vivo* observations of others (Tower, 1958c), but it did not occur to me that this key metabolic inhibitor could provide more than experimental laboratory interest. I did pass on to Louis Sokoloff my findings and interests; fortunately, he conceived of the usefullness of 2-DG for measuring regional and local cerebral blood flow and glucose consumption. He generously acknowledged my early assist but surely did a marvelous job of developing the method for *in vivo* clinical studies, especially with adaptations to positron emission tomographic (PET) procedures (Sokoloff, 1989).

Administrative and Organizational Activities

By the end of the 1960s my activities had shifted more to administrative and organizational aspects. These had begun modestly after my move to the NIH. I was promptly enlisted as a member of the Neurology Study Section in the NIH Division of Research Grants (DRG). They needed neurochemicàl expertise, which I attempted to provide during the period 1955–1961 (twice the usual tour of duty) until the DRG persuaded Heinrich Waelsch to join the study section in my place. During this period training fellowships were initiated under Elizabeth (Betsy) Hartmann, with the unique feature of personal interviews with each candidate. The

Neurology Study Section with Thomas O'Brien as executive secretary enjoyed many distinguished members, including in my era Frank Forster, Ray Snider, Bob Galambos, and Paul Bucy. The service on the study section was rather time-consuming (in terms of "homework") but one achieved a wonderful overview of the research field in the neural sciences. At the NIH I found myself recruited to chair the NIH Safety Committee (until 1967). When the NINDB program started in 1953, my unit was a section under Clinical Director Milton Shy, whereas the basic research units were administered jointly for NINDB anf NIMH by Seymour Kety and later Bob Livingston. In 1960 the basic research units were split between the two institutes and the neurochemistry groups joined as the Laboratory of Neurochemistry, NINDB. The lab had four sections: lipid chemistry under Roscoe Brady; cytochemistry and enzyme chemistry under Wayne Albers, my section on amino acids and electrolytes; and muscle chemistry under Beni Horvath (shortly succeeded by Eberhard Trams, with emphasis on membrane chemistry and ectoenzymes). I was asked to become chief of the laboratory, a post I held until 1973.

Like most laboratories, we recruited from the pool of research fellows who became available under the Selective Service (military) draft system then in operation. Graduate students (M.D. or Ph.D.) could satisfy their 2-year draft obligation by service on active duty in the U.S. Public Health Service Commissioned Officer Corps, while assigned to clinical or research billets at the NIH. Since our lab sections were relatively small, we were only able to recruit a few such fellows, but the quality of the available candidates was very high. During the 1960s, we recruited among others the following: lipid chemistry, Bernard W. Agranoff (now a professor at Michigan), Joseph D. Robinson (now a professor at the State University of New york at Syracuse), Julian Kanfer (now a professor at the University of Manitoba), Edwin Kolodny (now a professor at New York University); cytochemistry, Stanley Fahn (now a professor at Columbia P & S), George Siegel (now a professor at Loyola-Stritch, Chicago), Frederick Samaha (now a professor at Pittsburg); amino acids and electrolytes, Guy McKhann (now a professor at Johns Hopkins), John Wherrett (now a professor at Toronto), Robert Bourke (formerly a professor at Buffalo and Albany), and George Allen (now a professor at Vanderbilt). These are only a sampling. In my section we also had Michael Sporn (now program chief, NCI, NIH), Wesley Dingman (private psychiatric practise), Homer Kniseley (now a professor at the University of Florida), and Thomas Gill (now a professor at Oregon). All of us were ably backed up by our laboratory assistants: Edmund Peters, George Koval, Carl Lauter, Roy Bradley, Jane Quirk, and Oscar Young. These listings are incomplete and cannot do justice to the many contributions made by these researchers. The section heads benefitted immensely and we take pride in the record established during this period—truly a golden age for all of us at the NIH (Tower, 1985).

I must include here one anecdote to broaden our perspectives. Wayne Albers was immersed in studies on the nature and mechanisms of action of the Na^+- and-K^+-activated ATPase responsible for operating the cation pumps across neural and other cell membranes. A good source for the enzyme was the electroplax of the freshwater eel *Electrophorus electricus*. Its electroplax represents modified neuromuscular junctions, providing a series of electrode-like nerve endings that can deliver a stunning electric shock of hundreds to thousands of volts (designed to stun the eel's prey). We contracted for several large (8–10 ft.) eels to be flown to us from their native Amazon River habitat. They were shipped in 55-gallon metal drums via Kennedy Airport in New York City, in February, in below-freezing weather. As the ground crews started to wrestle the drums under cover, they were knocked flat by the 1000-V impulses through the uninsulated drums. The crews refused to handle them further, so our lab crew had to requisition a truck, drive the 3 or 4 hr to Kennedy, and claim the shipment, which by then consisted of eels frozen to death. You can be sure that the next time the eels arrived safely and were ensconsed in the U.S. Department of Commerce Aquarium in downtown Washington, DC. They proved to be a popular attraction, especially when the tank was fitted with a voltmeter to record the electroshock when the eel was challenged with a metal rod. These electroplaxes proved to be a rich source of the ATPase enzyme.

When we started out at the NIH there was a tendency to limit travel, especially meeting travel, but by the mid-1960s most of us were active in relevant national and international societies. The American Academy of Neurology was on the scene early with the promotions of sections as a means of stimulating professional education. With Maynard Cohen and Elizabeth Roboz-Einstein, 1 joined in starting a section on neurochemistry, which first met at the Boston meeting in 1958. We organized a symposium, and I made my first historical foray by giving a paper on the origins and development of neurochemistry (Tower, 1958d). Francis Schmitt, together with John Nurnberger and Saul Korey, organized a series of symposia, and it was there that Eugene Roberts presented much of his early data on GABA. Internationally, the neurochemists joined with Pergamon Press (Oxford) to launch the *Journal of Neurochemistry*. A series of international symposia were organized by Jordi Folch-Pi, Heinrich Waelsch, Seymour Kety, Derek Richter Henry McIlwain, and others. In 1958, I was invited to Vienna to a symposium,"Biochemistry of the Central Nervous System," at the Fourth International Biochemical Congress. I was also invited to the Third International Neurochemical Symposium in Strasbourg "Chemical Pathology of the Nervous System," with Paul Mandel as host–organizer. These two invitations for the same summer enabled my wife and I to plan a small tour of Europe to Norway, England, Austria, West Germany, Switzerland, and France—the first of several such opportunities. At home,

in leave time, Arline, Debbie, and I toured much of the United States by car (primarily to national parks), and Arline and I joined my parents and my two brothers and spouses on a Caribbean cruise aboard the 116-foot schooner *Panda* (from Martinique to Grenada with special stops at Bequia and the Tobago Keys).

A round-the-world trip developed in 1967, based on the need for me to travel to Israel to check on a counterpart funding contract and an invitation to me to attend and lecture at the Japanese Pharmacological Society annual meeting at the Japan Medical Congress in Nagoya. Because in the course of Roscoe Brady's investigations of the hereditary lipid storage diseases (Tay-Sachs, Niemann-Pick, Gaucher, etc.) he needed radioactively labeled substrates for the missing or attenuated enzymes characteristic of each disease, and because the world authority for the organic chemical synthesis of such compounds was David Shapiro at the Weizmann Institute in Rehovat, Israel, our lab contracted with Shapiro to synthesize the substrates, with the costs defrayed by use of the so-called PL–480 counterpart funds. The U.S. Congress approved supplies to Israel to be paid for in Israeli currency deposited for use by American officials for scientific, agricultural, etc. purposes. The contract with Shapiro required a project officer from the United States to evaluate progress; Brady and I filled that role, and it was my turn in early 1967. I traveled to Tel Aviv and was quartered at the Weizmann Institute. The project was progressing well. Shapiro arranged for me to drive with his lab assistant to Jerusalem (then still a divided city), Galilee, Nazareth, and the Golan Heights. Even a relatively naive tourist such as me could readily appreciate the problems that both Israelis and Arabs faced. I left Israel only a few weeks before the outbreak of the 1967 war. My further travels were via Beirut, Lebanon, to India, Bangkok, and Japan. I experienced the problems of traveling from Israel to an Arab country—flying to Cyprus, waiting all day to fly on to Beirut, and carrying two passports so as not to show an Israeli visa at an Arab border. I was met at Beirut airport by my good friend Fuad Haddad, late of Montreal and the MNI and the Middle East's first neurosurgeon (at American University in Beirut).

Let me digress for a moment to recall that a few years later I traveled to Shiraz in Iran to participate in a workshop organized by the International Brain Research Organization (IBRO). This was a unique gathering because it succeeded in bringing together scientists from every "Arab" country in the Middle East (including Turkey and Pakistan) plus several scientists from Israel. This was the first such "ecumenical" workshop on brain research. At the meeting there were discussions about establishing a brain research center, probably in Beirut, funded by part of the oil profits accruing to some of the emirates and including scientists from Israel. It was an exciting prospect. Alas, it was not to be because the Shah of Iran was deposed and Lebanon disintegrated into civil war.

Nevertheless, we were able to savor the exquisite gardens of Shiraz; visit the imposing ruins of the Persian capital of Persepolis, destroyed by Alexander the Great—the tents still in place for the Shah's celebration of its 5000th anniversary; and visit the many mosques and palaces in Isfahan.

In my 1967 world trip I flew from Beirut to New Delhi; in doing so, one leaves the West behind and enters the orient. In those days, I flew Pan American Airways, which then operated daily round-the-world flights both eastward and westward. At Beirut, going east, the plane was modified by taking out about eight rows of rear seats to accommodate chests of food, water, and other supplies to last until the flight reached Tokyo. While in India I visited New Delhi, Agra, the extraordinary Taj Mahal, and Kathmandu, Nepal, and spent about a week in Vellore (inland from Madras) at the Christian Medical College. My good friend (from MNI Montreal days), Jacob Chandy, India's first neurosurgeon, was then also dean and chief of the neurology services at the college. I stayed with the Chandys and learned from Mrs. Chandy how to make a proper Indian curry. She grew all the many ingredients (up to 30 or 40); her neighbors came daily to gather the spices needed for that day's curry. The institution at Vellore was founded by an American medical missionary, Dr. Ida Scudder, at the beginning of this century to provide especially for the medical care of women. Now it is a flourishing medical school, nursing school, modern hospital, and medical outreach institution (with traveling outpatient clinics). Indeed, neurochemistry was well represented there by Bimal Bachhawat, one of India's first scientists in that field.

Eventually, I reached Japan at Nagoya, where I was met by Professor Shiro Hisada, then president of the Japanese Pharmacological Society. My hosts offered to organize sight–seeing if I would specify my interests. In something of a quandry because of my ignorance of things Japanese, I opted for Japanese gardens. That turned out to be a good choice; I got to see beautiful gardens in Kyoto, Osaka, and Takamatsu (on the island of Shikoku). The meetings were enormous, so the peace and quiet of the gardens were especially welcome.

When I returned to the NIH I was offered the opportunity to act as director of the NINDB extramural programs (EP; grants and training) while its director Murray Goldstein took a sabbatical refresher year of clinical neurology at the Mayo Clinic. Frankly, I was curious to know how I would fare in such a managerial capacity.

Accordingly, I turned the lab over to Roscoe Brady and spent a year learning how to conduct the then $100+ million program in neuroscientific research and training (mid-1967 to mid-1968). It was quite an experience. Thanks to the seasoned and able staff I acquired a fair working knowledge of programs and procedures. Among my EP colleagues were Malcolm Ray

(research grants), Betsy Hartmann (training and fellowships), Mathilde Solowey and Elsa Keiles (large, program project grants), Larry Fitzgerald (contracts), and Mollyanne Harris and staff (grants processing). Murray Goldstein's secretary, Agnes Hardy, was especially helpful to me. I learned about study section operations (the EP operated several "captive" study sections), grants programming and processing, project site visits, oversight by the NINDB Advisory Council (which made the final funding decisions), and integration with the NIH DRG. One soon acquired special appreciation of peer-review and funding priority systems and of the constant budgetary woes that stemmed from insufficient funding from the administration, the Congress, and the NIH. At the year's end I went back to the lab to a somewhat less frenetic schedule. Later, when I became NINDS director, this year obviously stood me in good stead.

Meanwhile, my life was to be complicated in a different way. Heinrich Waelsch and Jordi Folch-Pi approached me to ascertain whether I would accept the post of chief editor (Western Hemisphere) of the *Journal of Neurochemistry* to replace Warren Sperry, who wanted to retire. It also developed that there were immediate problems that demanded a quick transition. I accepted the challenge and became the chief editor for the next 5 years (until the end of 1973). Derek Richter in the United Kingdom was chief editor (Eastern Hemisphere), and I recruited Louis Sokoloff to be Deputy Chief Editor (Western Hemisphere) and eventually to be my successor in 1973. The period 1968–1969 was crucial for the journal. It had been founded by Pergamon Press and initially the editorial board was chosen by Pergamon, in the person of its owner and operator Capt. Robert Maxwell. When the International Society for Neurochemistry (ISN) appeared in the mid-1960s, it informally adopted the journal as its official organ. In 1968 problems in financial dealings beset Pergamon Press, there was an attempted corporate takeover, trading of its stock on the London exchange was suspended, and Capt. Maxwell was temporarily ousted. The future of the *Journal of Neurochemistry* was seriously threatened, such that the acting chairman of Pergamon approached Jordi Folch-Pi (as ISN secretary) to offer transfer of copyright and ownership of the journal to the ISN for $1.00 and a continuing contract with Pergamon to publish the journal. The journal editors (Richter and Tower) and the ISN Council [headed by Roger Rossiter (Canada), Jordi Folch-Pi (USA), and Derek Richter (UK)] considered the proposal and recommended acceptance. Thus, at the onset of my chief editorship the journal became the property of the ISN and its official organ. Captain Maxwell eventually was restored to his former position at Pergamon Press but never quite accepted the transfer of the journal to the ISN and its independent authority to select the editorial board. By the expiration of the publishing contract in 1973, the ISN sought other publishers, eventually settling on Raven Press (now part of Lippincott, Williams & Wilkins).

Aside from the foregoing contretemps, the actual business of editing a journal such as the *Journal of Neurochemistry* was a very time-consuming task. At that time, approximately 1,200 manuscripts per year were handled by my editorial office. I spent many nights, weekends, and holidays, and even some work hours, on editorial demands. I found myself rewriting some of the submissions to render them more readable and more oriented to the point of the research. Many authors thanked me; I received only one written objection to my editing. Clearly, the editing cut quite deeply into my own research time, as I began to shift out of the laboratory research mode. However, the editing kept me au courant for essentially everything that was happening at that time in neurochemistry. One must not overlook the vital contributions made by the board of editors in evaluating submitted manuscripts and recommending their dispositions. Certainly, the journal established an important position in the world's scientific literature.

At this same period, beginning in 1968, Jordi Folch-Pi (Harvard; McLean Hospital), Wallace Tourtellotte (Michigan), and I (NINDB, NIH) circulated a letter to the 119 American members of the already established ISN to explore the possibility of establishing an American Society for Neurochemistry (ASN)(Tower, 1987). We received 101 replies in favor of an ASN, with nominations for members of the organizing committee. The committee consisted of Bernard Agranoff (Michigan), Jordi Folch-Pi, Martin Gál (Iowa), Seymour Kety (Harvard), Abel Lajtha (Institute for Neurochemistry, Ward's Island, NY), Francis LeBaron (New Mexico), Henry Mahler (Indiana), Guy McKhann (Hopkins), Eugene Roberts (City of Hope, Duarte, CA), Wallace Tourtellotte, Donald Tower, and Frederick Wolfgram (UCLA). Responses were enthusiastic, although there were alternative ideas, including the move by Ralph Gerard (Chicago) to join in founding the Society for Neuroscience (in 1969). The ASN organizing committee met twice, chose Jordi Folch-Pi as provisional secretary and me as provisional treasurer, and planned for the first Society meeting in Albuquerque, March 16–18, 1970. I was charged with incorporating the ASN, a process completed by our legal representatives in August 1969. Folch-Pi and I continued as ASN secretary and treasurer, respectively, and Fran LeBaron was elected president at the Albuquerque meeting. A significant initiative by the ASN was the agreement to sponsor publication of a textbook, *Basic Neurochemistry*, now in its sixth (1999) edition. The ASN has grown and flourished with annual meetings throughout the Western Hemisphere (United States, Canada, Mexico, Venezuela, and, in 2001, Argentina).

For me, another major event took place in Novermber 1969, when five U.S. neurochemists participated in an exchange mission to the Soviet Union, under the renewed exchange agreement between the United States and the USSR. We were aware of a considerable tradition of research on

chemistry of the nervous system dating back to the 1920s and the subject of five Soviet conferences on neurochemistry in Kiev (1953 and 1957), in Yerevan (1962), in Tartu (1966), and Tbilisi (1968), each with publication of proceedings. Thus, we sought to visit most of the active centers to learn more about their current research. Somewhat to our surprise, our proposal was promptly approved. Our delegation comprised Louis Sokoloff (NIMH–NIH), Bernard Agranoff (Michigan), David McDougal (Washington University St. Louis), Guy McKhann (Johns Hopkins), and myself as chairman. We arrived at Sheremetyevo airport in Moscow on a cold, snowy November afternoon, but there was no one (Soviet or U.S. Embassy) to meet us. With some reluctance the Intourist representative, reinforced by the representatives of Finn Air and Pan American, put us in touch with the Soviet Ministry of Health, only to learn that they had not been notified about our coming and thus had made no arrangements for us. They suggested we return home but were kind enough to locate the U.S. Embassy's Scientific Attaché William Harben, who also was unaware of our intended arrival. He did manage to find us somewhat primitive but passable hotel accommodations near the television tower on the outskirts of Moscow. A few days later we learned that the cable of notification was not sent from the Office of International Health at DHEW in Washington until after our initial briefings at the Soviet Ministry of Health. Otherwise, our trip through the USSR went quite smoothly. We met with Dr. Dmitri Orlov, Deputy Chief of Foreign Relations, at the Ministry of Health the morning after our arrival. At first they protested that it was impossible to accommodate us and that we had not allowed enough time for travel and visits to laboratories. I had come armed with an *Official Airlines Guide* (OAG) and an outline of flights to the various visit sites and was able to persuade them that the itinerary was quite feasible. The OAG was also helpful in circumventing the Soviet system of funneling all flights via Moscow and listing flight times all on Moscow time, despite the fact that the USSR covered 11 time zones. To our surprise, with credit to Orlov and his staff, we prevailed to begin our tour.

We began in Moscow with visits to several research groups, highlighted by a half-day at the Institute of Molecular Biology, directed by academician V. A. Engel 'gardt, who was responsible for the resurgence of molecular biology in the USSR after the Lysenko episode. Engel 'gardt was an early worker in neurochemistry and a founding editor of the *Journal of Neurochemistry*. This group included academician A. E. Braunshtein and was most impressive. Our next stop was at Novosibirsk in central Siberia to visit the Akademgorodok or academic science city on its outskirts. The science city included 22 research institutes, a large computer center, and a university. We witnessed online computer analyses of cortical evoked potentials, and we toured the computer center—a very impressive facility, with its major dedication to weather forecasting, a major concern in such

an extensive country. Leningrad (now St. Petersburg) was next. Our visit was introduced by a briefing on the World War II Siege of Leningrad, whose defense was a source of real local pride. We met with three excellent groups: academician Ye.M. Kreps at the Sechenov Institute of Evolutionary Physiology and Biochemistry, Prof. N. N. Doemin in neurochemistry at the Pavlov Institute of Physiology, and Prof. M. I. Prokhorova at the Zdanov University Institute of Physiology (she was a dynamic leader of a very active group). From Leningrad we flew to Kiev in the Ukraine to the Institute of Biochemistry to visit academician A.V. Palladin, who at age 84 was still a vigorous leader of Soviet science. Palladin had done neurochemical research since the early 1920s and was instrumental in organizing the meetings mentioned previously. From Kiev we flew to Tbilisi, capital of the Georgian SSR, to visit the Insitute of Physiology Department of Biochemistry under Prof. P. A. Kometiani. We missed seeing Prof. G. I. Mchedlishvili, who headed the cerebral circulation lab. Finally, we flew to Yerevan, capital of the Armenian SSR, to visit the Institute of Biochemistry directed by Prof. H. Ch. Buniatian. The institute was about to move into extensive, newly constructed quarters. This group was the largest unit in the USSR then devoted to neurochemical research. It included Dr. A. A. Galoyan, now institute director and already know for his discovery of hypothalamic hormones with actions on coronary heart vessels. Buniatian was a gracious host, inviting us to his house for dinner and in subsequent years paying visits to the United States and organizing symposia in Yerevan. Our group was not able to visit smaller groups in Khar'kov (Ukraine), Tartu (Estonian SSR), Rostov-Don, or Minsk (Byelorussian SSR), among others. A fairly detailed report of the delegates' visit to the USSR and its various neurochemical research groups has been published (Tower, 1970). The U.S. delegation had little time for sightseeing or other cultural inputs. We did visit the Kremlin cathedrals and museums and the Tretyakov galleries in Moscow, the Hermitage museum in Leningrad, St. Sophia and the Lavra Pechersky (monasteries) in Kiev, the old Georgian capital of Mtskhet (outside Tbilisi), and the memorial to the Armenian martyrs and the Matenadaran manuscript library in Yereva. We also attended ballet and opera at the Bolshoi and at the Kremlin Congress Hall, respectively, and dinner at several specialty restaurants.

Clearly, our exchange mission was a success. We obtained a reasonably comprehensive view of Soviet neurochemical research, with the impression that Soviet neurochemistry in most cases compares well with Western neurochemistry. We were especially impressed by the excellence of the younger professionals, most of them conversant with English and well trained scientifically and enthusiastic about their research. The Soviet scientists that we met were warmly and generously hospitable and enthusiastic about the exchange program. In the era in which we traveled, news

blackouts deprived the Western visitor of current events. However, our Soviet hosts kept us informed, for example, of the U.S. Apollo-12 flight, toasting its success in landing on the moon and its return to Earth. In two subsequent trips to the USSR—one in 1973 as an invited participant in a symposium organized by Buniatian in Yerevan (Armenian SSR) (with an excursion afterwards with Abel Lajtha to Tashkent and Samarkand in the Uzbek SSR) and the other in 1975 as a member of the exchange delegation on Multiple Sclerosis to the Soviet Academy of Sciences in Moscow—I found no reason to modify or change the foregoing impressions generated during our initial visit in 1969.

Years as Director of the Neurology Institute

In the early 1970s, the NINDS faced budgetary problems and the imminent departure of its third director, Edward (Ted) MacNichol. A search committee for a new director was initiated in late 1971 or early 1972. This committee gave up after a year's search and recommended that an acting director be appointed while the search for a permanent director resumed. I was approached by the acting director of the NIH John Sherman: Would I be willing to serve as the acting director of the NINDS for a year? Finding myself at a pause in my research, I agreed to do so for the period May 1973 to April 1974. At the end of April 1974 the search committee was still searching. Therefore, Robert Stone, by then director of NIH, asked me to be considered for permanent NINDS director. At that moment it seemed the proper course, and I said yes. Two of us at the NIH were proposed as candidates; after many people throughout the country were consulted, I was designated and my name was sent downtown to navigate the quasi-political clearance process that such applications required.

My nomination was promptly rejected at the White House liaison office in DHEW. Bob Stone (NIH director) called me to tell me that a letter had been sent a year earlier by one of the NINDS advisory council members to the White House to the effect that I should not under any circumstances be appointed Institute Director. The council member in question had taken exception to my remarks to the council about the problems Watergate posed for us and objected as a staunch Nixon Republican. Bob Stone offered to submit his resignation to emphasize his insistence on my appointment. I urged him to wait while I called the council member, who was appalled and said the letter never should have been sent and promised it would be withdrawn. So it was, and I became director of the NINDS in mid-1974.

I inherited a good staff: Eldon Eagles as deputy director, Eckart Wipf and subsequently Richard Sherbert as executive officers, Robert Sithins and subsequently William Matthews as budget officers, Ruth Dudley as information officer, Murray Goldstein as director of extramural programs,

and my secretary, Lorraine Griffith. My tenure began with two major problems, budget and personnel. The budget was then at a low ebb at $143 million, less than one-seventh of what it is today (FY 2000), due partly to executive (White Hosue) and congressional withholdings and economizings and partly due to loss of public confidence. Even though we finally managed to secure $254 million or almost double the 1974 figure by 1981, when I retired, in terms of constant 1974 dollars (correcting for inflation) we actually lost money—down to $139 million in constant 1974 dollars in FY 1981. In the public sector we had lost some of the support from Mary Lasker and associates—an alienation that I worked hard to erase. My efforts were successful; in fact, I was appointed to service on the Lasker Awards Jury, a responsibility that I valued and enjoyed. Indoctrination into the budget process took early priority since in the spring of 1974 I immediately plunged into the congressional budget hearings process, testifying before the appropriations subcommittees for Labor-DHEW in the House before Chairman Daniel Flood (from Scranton, PA) and in the Senate before Chairman Warren Magnuson (state of Washington). Other key congressmen at the time were Paul Rogers (Florida) and Sylvio Conte (Massachusetts). My first Senate hearing was chaired by Senator Mark Hatfield (Oregon), ranking Republican on the subcommittee. It was a tough session, but with help from my backup staff I emerged unscathed. As I left the hearing room a lady spectator congratulated me for doing so well before Hatfield, the Senate's best debater. Because of the varied nature of NINDS research needs, my predecessors had encouraged the formation of a national committee whose members represented all the neurological and communicative (sensory) disorders. This I also encouraged in order to promote congressional testimony on the problems to be addressed and the funding needed to research them. One special problem was the training of new clinical and basic researchers. The original training programs of the 1950s and 1960s had been phased out as administration and Congress sought to rein in the ever-burgeoning NIH budget—the idea being fewer science trainees meant fewer applicants for research funds. It is said that the then director of the NIH, James Shannon, in a moment of weakness, originated this suggestion. In any case, it required vigorous effort and considerable ingenuity to reverse this negative momentum.

The personnel problems facing the NINDS were twofold. One facet was the collaborative and field research program, the Perinatal Project, conceived by the first NINDB director, Pearce Bailey, and developed by its second director, Richard Masland. Basically, this project recruited approximately 50,000 pregnant mothers and their approximately-60,000 babies to study various neurological problems during pregnancy and the perinatal periods. As it eventually turned out, this was an enormously successful project, providing a huge body of data computerized for continued ready

reference. However, at the time the NIH administration regarded it as a bottomless pit into which funds were committed. I was told that if I shut the project down, the NIH would provide more personnel slots to the NINDS. I countered by pointing out that I had the authority to terminate the project immediately, but I had nowhere to place approximately 100 people in the project who had civil service tenure; they could not be summarily fired. The NIH finally appreciated this real problem and with us worked out an intelligent solution. Some of the perinatal groups joined our intramural program and others went to our extramural program so that an orderly and mutually satisfactory termination of the Perinatal Project could ensue. The database persists such that when a question was raised about the prevalence of simian SV-40 virus in blood samples from polio-immunized patients in the project, it was possible to collect the data from stored blood samples.

The other major personnel problem related to the NINDS intramural program, which was struggling and did not enjoy a good image with the NIH administration. I was able to recruit new people into the program and reverse its image. The problem, however, was symptomatic of more general problems throughout the NIH. Its staff was growing older, yet orderly retirements were nullified by dispensing with age "discrimination." Federal salaries, especially for medically trained personnel, were no longer competitive with the private sector. Also, the attractiveness of the NIH as a place to do research had lessened. These are still problems with few long-range solutions in sight.

An Institute Director is inevitably involved in many outside activities. During my tenure, we were faced with the proliferation of congressionally mandated commissions on specific diseases, including, in our case, multiple sclerosis, diabetes (especially neuropathies), epilepsy, and Huntington's disease and related disorders. These commissions were time-consuming and not well supported by DHEW: no resources for funding, housing, or staffing, and long delays on charters and on appointment of members. Nevertheless, we profited by working with dedicated commission members: Charles Meares and Harry Weaver for Multiple Sclerosis, Ellen Grass for epilepsy, and Marjorie Guthrie and Nancy Wexler for Huntington's disease. Among the outcomes were the anticonvulsant drug development and screening program (leading to introduction of carbamazepine, clonazepam, and valproate, greatly aided by our staff under Kiffin Penry) and the survey of the Huntington's disease focus on Lake Maracaibo in Venezuela. Another research initiative concentrated on CNS regeneration, with particular reference to spinal cord injury and paraplegia and to the fact that central regeneration could indeed occur. Then we were challenged by Senator Goldwater (Arizona) to "empty the schools for the deaf" by promoting development and use of the cochlear implant devices. This turned out to be more complicated than the original

proponents anticipated, but today the latest versions of these devices have achieved some surprising successes. In another area, the computerized tomographic (CT) scanners and derivative imaging devices (Magnetic resonance imaging), Positron emission tomography (PET), etc.) have assumed special significance as research tools. The NINDS decided not to embark on promotion of CT scanners since the Hounsfield devices quickly became commercially and diagnostically successful. However, given the major contribution of the 2-DG method for metabolic and circulatory studies *in situ* and *in vivo* by Louis Sokoloff and colleagues, we did embark on a program of support for centers to exploit the research potentials for positron emission tomography PET. The NINDS advisory council with staff and special consultants evaluated the procedures and approved issuance of a Request for Applications. Thus, in the 1978–1979 period eight centers were funded at an initial level totalling $10 million. This proved to be a most promising investment. At this time Drs. Robert Katzman and Robert Terry, both at the University of California at San Diego, urged us to give greater attention to Alzheimer's Disease, in their view a serious but neglected problem. We brought together several lay groups and relevant NIH institute representatives to launch an overall national organization to provide liaison between patients and families and the researchers. This initiative has proved to be very valuable and successful to all concerned.

In quite a different context, the NINDS was designated by the World Health Organization (WHO) as one of its Collaborating Centers for Research and Training in the Neurosciences. Many of our senior staff (notably Murray Goldstein) were involved. The liaison for WHO was Dr. Liana Bolis, who organized many planning and programmatic meetings in such places as Abidjan (Ivory Coast), Marseilles, Geneva, Firenze, Montreal, Lima, Ibadan (Nigeria), and Dakar (Senegal). At the behest of WHO, I made trips to Egypt, India, and Manila to evaluate potential additional centers, and with William Feindel (then director of the MNI) and Liana Bolis, I traveled to the Peoples' Republic of China for the same purpose (Tower and Feindel, 1980). Our visit to China was limited to Beijing and Shanghai, where most of the potential centers were located. This was a most interesting trip; we were impressed by the prevalence of English-speaking and understanding and by their acquaintance with and utilization of recent techniques published elsewhere. Acupuncture was much in evidence. A special dividend of our trip was a drive to Tienjin (north of Beijing) to meet Madam Chao, the widow of Chao Yi-cheng, who had been trained by Penfield in Montreal and was the founder of Chinese neurosurgery.

Parenthetically, I note that one of our intramural scientists, Carleton Gajdusek, won the 1976 Nobel Prize in medicine for his discovery of the transmissible nature of the atypical "slow viruses" of the Kuru and

Creutzfeldt–Jacob types (Tower, 1977). Both Gajdusek and Roscoe Brady have been elected members of the U.S. National Academy of Sciences. Also ,as the two top administrators of the NINDS, both Murray Goldstein and I were promoted to flag rank of Assistant Surgeon General (Rear Admiral) in the U.S. Public Health Service Commissioned Corps, and both of us were awarded the Distinguished Service Medal, the highest decoration for PHS officers. I must note, with respect to Gajdusek's Nobel prize that at his invitation I traveled to Stockholm (at my expense) to attend the Nobel ceremonies. Traditionally, it is on the 10th of December (Alfred Nobel's birthday), when Stockholm is cold, snowy, but very festive. I enjoyed the experience—as close as I shall come to a prize. Incidentally I count seven Nobel laureates as good friends: at the NIH, the late Christian Anfinsen, Marshall Nirenberg, Julius Axelrod, and Carleton Gajdusek; plus Roger Guillemin (now at the Whitter Institute, La Jolla, CA), David Hubel (Harvard), and Stanley Prusiner (University of California at San Francisco).

In these latter accounts of my 8 years as institute director I have abbreviated or omitted much, especially with respect to personnel involved both within the Institute and the outside advisers who served the Institute and me so well. In my last annual report as director, dated September 30, 1980, I tried to cover such matters in full detail. The interested reader is accordingly directed there (Tower, 1980).

Retirement and Historical Research

Nearing the end of my eight year as director, I began to plan for retirement. It seemed to me that I could return to the laboratory only with difficulty and much reeducation. Also, I felt that 8 years as director was enough. Inevitably, there comes a time when a fresh mind and fresh approaches are needed. Therefore, ending my career at 30 years of active duty service (navy and PHS) and nearly 40 years total service seemed the appropriate choice. It meant quite a shift in emphasis to travel, golf, photography, historical research, and perhaps some consulting. My wife Arline and I began with travel to Australia and New Zealand. In a promotional program Pan American Airways issued "twofers"—a full fare paid ticket and a free ticket for a companion wherever Pan Am flew. The Antipodes were the farthest away and we wanted to visit them. The only key planning was for us to be on Heron Island on the Great Barrier Reef when the tide was low at midday so we could walk out onto the reef around the island. Calls to the Australian embassy revealed a total lack of tidal information. Therefore, I turned to my colleague Clarence J. (Joe) Gibbs in —Gajdusek's lab and a naval reservist: Would the U.S. Navy know about Heron Island (Australia) tides? Yes they did, so our planning could go forward during November 1980 to visit Sydney, Brisbane, Gladstone,

Heron Island, Auckland, Christchurch, Queenstown, and Mt. Cooke (including ski-plane landing on its glacier). Our homeward journey detoured us to the Hawaiian Islands. Another trip in 1993 took us to Suez in Egypt where we boarded the ship *Illyria* for a 30-day cruise to Yemen, Somalia, Kenya (and the Masai Mara game reserves), the Seychelle Islands, the Maldive Islands, Sri Lanka, the Madras area of India, Banda Aceh in Sumatra, and disembarkation in Singapore. We flew home via Bangkok and Hong Kong. I have many travel favorites and special photo opportunities, but none exceed this trip to so many unusual places.

At home I began to delve into the early period in the history of neurochemistry. I had learned about Johann Thomas Hensing, professor at the University of Giessen in Hesse-Darmstadt, Germany, from Thudichum's historical appendix to the 1901 German edition of his monograph on the chemical constitution of the brain ((Thudichum, 1901). My wife and I visited Giessen and neighboring Marburg in 1958, after obtaining a photocopy of the only known copy of Hensing's 1719 monograph *Cerebri Examen Chemicum, ex eodemque Phosphorum singularem omnia inflammabilia accendentem*. The library personnel at Giessen found for me Hensing's "Personalakten" (personnel file, in the form of letters hand-written in German script) and other publications by Hensing. He was a practicing physician and held appointments as Prof. extraordinarius (associate professor) of medicine (from 1717) and Prof. ordinarius (full professor) of natural and chemical philosophy (from 1723). After two attempts to obtain translations of the original Latin monograph, I undertook my own translation. By the end of 1982 I had put together a monograph delineating an historical perspective for the seventeenth century, an account of the city of Giessen and its university, a biography of Hensing, and the transcription of the original Latin set opposite my English translation to serve as a sourcebook. Many people helped me, most notably Mrs. Dorothy Hanks, then of the History of Medicine Division, National Library of Medicine; the late Dr. Theodor Wanko (then of the Ophthalmology Branch, NINDB, NIH); and the staff of the library at the University of Giessen (now Justus-Liebig-Universität). The completed monograph was published by Raven Press in 1983 (Tower, 1983). The work was well received and was awarded the Award of Distinction in History by the Justus-Liebig-Universität in 1984. Hensing's chemical laboratory was located in his house, much to the distress of his wife. From his chemical analyses, Hensing reported "copiam olei in cerebro" (copious amounts of oils or fats in brain) and the isolation of elemental phosphorus—a singular fiery phosphorus—the first specific substance to be isolated from brain.

In the process of gathering material for the monograph on Hensing, I acquired data and documents on many other contributors to brain chemistry. Prominent among these were the works of five French chemists working at the time of the French Revolution and Restoration

(1791–1841): Michel-Augustin Thouret (1749–1810), physician and chemist; Antoine François de Fourcroy (1755–1809), physician, chemist, and patriot; Nicolas-Louis Vauquelin (1763–1829), initially Fourcroy's lab assistant and later master chemist; Jean-Pierre Couerbe (1805–1867), pharmacist, chemist, and latterly vintner in his own right; and Edmond Frémy (1814–1894), chemist and academician. Their respective scientific reports together constituted a related sequence of chemical analyses on human brain. (With the exception of Thouret's studies on cadavers, the sources of these fresh human brains were not specified!) I translated the five reports from the original French and prepared another monograph also as a sourcebook, with introductory narratives to accompany the original French texts and the English translations on facing pages. Publication was by Raven Press (Tower, 1994), supported by a subvention from the International Society for Neurochemistry. Collection of much of the background material was facilitated by my travels to meetings of the Council of IBRO, usually held in late spring in Paris with Mary A.B. (Mollie) Brazier as secretary-general. She usually found travel funds to Paris so that I was able to take leave after the meetings to look up historical materials. In addition to the Parisian locales, I traveled to Normandy (to St. André-d'Hébertot, Vauquelin's birthplace), and to the Haut-Médoc in the countryside outside Bordeaux, and to Vertheuil (Médoc-Gironde), the birthplace of Couerbe, and La Gravière, his estate outside Vertheuil. Much of my information on Couerbe was obtained from local archives by Mme. H. Poitevin, historian for Vertheuil. Several of the contributions by these five chemists were noteworthy. Fourcroy reported that cerebral matter contained a coagulable material behaving like egg white and thus was the first chemist to count albumin (protein) as a cerebral constituent. Fourcroy and Vauquelin were the first to recognize organic phosphates in the -C-P compounds in carp roe, and they also identified urea as the mammalian excretory form for nitrogenous materials. Vauquelin extended the phosphate studies to human brain tissue, leading to his conclusion that phosphorus was combined with fatty substances of the brain (today our phospholipids). Vauquelin reported his analyses in tabular form—the first modern quantitative data. Finally, there was Couerbe, who introduced quantitative elemental analyses for brain tissue samples. An example was his isolation from brain of cholesterol and his analyses (in 1833) that compare closely with Chevreul's analyses on gall stones (1815) (Tower, 1994, p. 178). Couerbe also tried to relate brain levels of phosphorus to mental states (imbeciles vs insane)—the first such attempts, in which Couerbe sought to propose phosphorus as an excitatory agency or element in cerebral functions.

Other historical examples have gained my attention (Tower, 1991), but I leave these two books as sufficient indications of my interests and of the wealth of data to be exploited (Tower, 1983, 1994). When not otherwise

engaged, my wife and I delved into our family genealogies, which are now reasonably complete and in the hands of our grandchildren (Tower, 1995). If one were to try to sum up a career such as mine, I suggest that the observation attributed to John Donne might be most appropriate:

> As the island of knowledge grows and expands,
> So also does the extent of the shoreline with the unknown.

Selected Bibliography

Allen GS, Tower DB. Acidic proteins in cerebral and hepatic microsomes: Isolation of a protein (AGL-40) composed primarily of glutamyl, aspartyl and lysyl residues with hematin binding properties. In Buniatian HCh, ed. *Voprosy biokhimii mozga* (Problems of biochemistry of brain), Vol 7, Yerevan; Armenian Academy of Sciences, 1972;69–81.

Bourke RS, Greenberg ES, Tower DB. Variation of cerebral cortex fluid spaces *in vivo* as a function of species brain size. *Am J Physiol* 1965;208:682–692.

Delgado-Escueta AV, Wilson WA, Olsen RW, Porter RJ, eds. *Jasper's basic mechanisms of the epilepsies*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.

Gentz J, Hamfelt A, Johansson A, Lindstedt S, Perrson B, Zetterström R. Vitamin B_6 metabolism in pyridoxine dependency with seizures. *Acta Paediat-Scand* 1967;56:17.

Gill TH, Young OM, Tower DB. The uptake of ^{36}Cl into astrocytes in tissue culture by a potassium-dependent, saturable process. *J Neurochem* 1974;23:1011–1018.

Hawkins JE, Sarett LH. On the efficacy of asparagine, glutamine, γ-aminobutyric acid and 2-pyrrolidinone in preventing chemically induced seizures in mice. *Clin Chim Acta* 1957;2:481.

Marie J, Hennequet A, Lyon G, Debris P, LaBalle JC. Le pyridoxino-dépendence, maladie métabolique s'exprimant par des crises convulsives pyridoxino-sensibles (première observation familiale). *Rev Neurol (Paris)* 1961;105:406.

McKhann GM, Tower DB. Gamma-aminobutyric acid: A substrate for oxidative metabolism of cerebral cortex. *Am J Physiol* 1959;196:36–38.

McKhann GM, Tower DB. The regulation of γ-aminobutyric acid metabolism in cerebral cortex mitochondria. *J Neurochem* 1961a;7:26–32.

McKhann GM, Tower DB. Ammonia toxicity and cerebral oxidative metabolism. *Am J Physiol* 1961b;200:420–424.

McKhann GM, Albers RW, Sokoloff L, Mickelsen O, Tower DB. The quantitative significance of the gamma-aminobutyric acid pathway in cerebral oxidative metabolism. In E Roberts E, ed. *Inhibition in the nervous system and gamma-aminobutyric acid*. Oxford: Pergamon, 1960;169–181.

Meiklejohn AP, Passmore R, Peters RA. The independence of vitamin B deficiency and inanition. *Proc R Soc B* 1932;111:391.

Peters EL, Tower DB. Glutamic acid and glutamine metabolism in cerebral cortex after seizures induced by methionine sulfoximine. *J Neurochem* 1959;5:80–90.

Ronzio RA, Rowe BW, Meister A. Studies on the mechanism of inhibition of glutamine synthetase by methionine sulfoximine. *Biochemistry* 1969; 8:1066–1075.

Sokoloff L. Circulation and energy metabolism of the brain. In Siegel GJ, Agranoff BW, Albers RW, Molinoff PB, eds. *Basic neurochemistry*, 4th ed. New York: Raven Press, 1989;565–590.

Sokoloff L, Lassen NA, McKhann GM, Tower DB, Albers W. Effects of pyridoxine withdrawal on cerebral circulation and metabolism in a pyridoxine-dependent child. *Nature (London)* 1959;173:751–753.

Thudichum JLW. *Die chemische Konstitution des Gehirns des Menschen und der Tiere*. Tübingen: Pietzcker, 1901;1–73.

Tower DB. The use of marine mollusca and their value in reconstructing prehistoric trade routes in the American Southwest. *Papers Excavators' Club* 1945; 2(3):1–56.

Tower DB. The use of mass Atabrine therapy for the control of malaria in a civilian population, Olongapo, Subic Bay. P.I. Report (restricted) to the U.S. Navy Bureau of Medicine and Surgery, 1946.

Tower DB. Structure and functional organization of mammalian cerebral cortex: The correlation of neurone density with brain size. *J Comp Neurol* 1954;101:19–51.

Tower DB. Discussion [A note on the clinical and pathological aspects of toxicity from "Agenized" proteins and methionine sulfoximine]. In Baldwin M, Bailey P, eds. *Temporal lobe epilepsy*. Springfield, IL: Thomas, 1958a;288–295.

Tower DB. The evidence for a neurochemical basis of seizures. In Baldwin M, Bailey P, eds. *Temporal lobe epilepsy*. Springfield, IL: Thomas, 1958b;301–348.

Tower DB. The effects of 2-deoxy-D-glucose on metabolism of slices of cerebral cortex incubated *in vitro*. *J Neurochem* 1958c;3:185–205.

Tower DB. Origins and development of neurochemistry. *Neurology* 1958d;8(Suppl. 1):3–31.

Tower DB. The administration of gamma-aminobutyric acid to man: Systemic effects and anticonvulsant action. In Roberts E, ed. *Inhibition in the nervous system and gamma-aminobutyric acid*. Oxford: Pergamon, 1960a;562–578.

Tower DB. *Neurochemistry of epilepsy: Seizure mechanisms and their management*. Springfield, IL: Thomas, 1960b.

Tower DB. *Tenkan no Seikagaku* (Biochemistry of epilepsy). (Mori A, Takasaka M, Nishimoto S, trans.). Osaka: Nagai-Shoten, 1964.

Tower DB. Neurochemical mechanisms. In Jasper HH, Ward A, Pope A, eds. *Basic mechanisms of the epilepsies*. Boston: Little, Brown, 1969;611–638.

Tower DB (ed.). *Neurochemistry in the Soviet Union*. Bethesda MD: DHEW National Institutes of Health (U.S. Government Printing Office), 1970.

Tower DB, Cerebral edema. In Albers RW, Siegel GJ, Katzman R, Agranoff BW, eds. *Basic neurochemistry*. Boston: Little, Brown, 1972;537–554.

Tower DB. The role of astroglia as modulators of neuronal function in cerebral cortex: Comparative data, observations *in vivo* and *in vitro* on fluid, electrolyte and amino acid interrelationships. In Buniatian HCh, ed. *Voprosy biokhimii mozga (Problems of biochemistry of brain)*. Vol 8. Yerevan: Armenian Academy

Tower DB, D Carleton Gajdusek MD.—Nobel laureate in medicine for 1976. *Arch Neurol* 1977;34:205–208.

Tower DB. Annual report of the director, NINCDS, October 1, 1979—September 30, 1980. [NIH Archives, 1980].

Tower DB. *Hensing, 1719. An account of the first chemical examination of the brain and the discovery of phosphorus therein*. New York: Raven Press, 1983.

Tower DB. The neurosciences—Basic and clinical. In Stetten D Jr, ed. *NIH: An account of research in its laboratories and clinics*. New York: Academic Press. 1985:48–70.

Tower DB. Career in neuroscience: Oral interview taped by Louise Marshall, Ph.D., for the UCLA Brain Research Institute Neuroscience Resource Project, Oral History Program, 1986.

Tower DB. Historical perspective. The American Society for Neurochemistry (ASN): Antecedents, founding and early years. *J Neurochem* 1987;48:313–326.

Tower DB. Cerebral circulation revisited: An historical essay [dedicated to Louis Sokoloff]. *Neurochem Res* 1991;16:1085–1097.

Tower DB. *Brain chemistry and the French connection 1791–1841. An account of the chemical analyses of the human brain by Thouret (1791), Fourcroy (1793), Vauquelin (1811), Couerbe (1834), and Frémy (1841)*. New York: Raven Press, 1994.

Tower DB. Genealogy of the Tower, Thompson, Bishop, Jones, Croft, Meadows, Holesworth, Fretwell, Waterman, Kennedy, Hochstetler, and related families, prepared for Kelsey Alden Fretwell and Lucas Tower Fretwell. [Privately produced for limited distribution.] 1995.

Tower DB, Bourke RS. Fluid compartmentation and electrolytes of cat cerebral cortex *in vitro*—III. Ontogenetic and comparative aspects. *J Neurochem* 1966;13:1119–1137.

Tower DB, Elliott KAC. Activity of acetylcholine system in cerebral cortex of various unanesthetized mammals. *Am J Physiol* 1952a;168:747–759.

Tower DB, Elliott KAC. Activity of acetylcholine system in human epileptogenic focus. *J Appl Physiol* 1952b;4:669–676.

Tower DB, Feindel W. Impressions of neurology and neurosurgery in the Peoples' Republic of China. *Ann Neurol* 1980;7:395–405.

Tower DB, McEachern D. Acetylcholine and neural activity II. Acetylcholine and cholinesterase activity in the cerebrospinal fluids of patients with epilepsy. *Can J Res E* 1949;27:120–131.

Tower DB, Peters EL, Wherrett JR. Determination of protein-bound glutamine and asparagine. *J Biol Chem* 1962;237:1861–1869. [The accompanying paper by Potts, Berger, Cooke, and Anfinsen on ribonuclease structure was published in the same journal issue, pp. 1851–1860.]

Tower DB, Wherrett JR. Glutamyl and aspartyl moieties of cerebral proteins: enrichment in membrane-containing microsomal subfractions. *J Neurochem* 1971;18:1043–1051.

Tower DB, Young OM. Interspecies correlations of cerebrocortical oxygen consumption, acetylcholinesterase activity and chloride content: Studies on the brains of the fin whale (*Balaenoptera physalus*) and the sperm whale (*Physeter catodon*). *J Neurochem* 1973;20:253–267.

Wanko T, Tower DB. Combined morphological and biochemical studies of incubated slices of cerebral cortex. In Cohen MM, Snider RS, eds. *Morphological and biochemical correlates of neural activity*. New York: Hoeber, 1964;75–97.

Wherrett JR, Tower DB. Glutamyl, aspartyl and amide moieties of cerebral proteins: Metabolic aspects *in vitro*. *J Neurochem* 1971;18:1027–1042.