Chapter 17

# Neuropathology

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Neuropathology has a long tradition at the Massachusetts General Hospital (MGH). Among the various anatomical pathology subspecialties at the MGH, it is the oldest, in terms of both dedicated subspecialty faculty and a subspecialty training program. In its extensive history it has demonstrated excellence in clinical care, education, and research, and many of its successes have been attributed to the extraordinarily close interactions between Neuropathology and its associated departments, initially Psychiatry and Neurology and later Neurosurgery, which continue to this day.

Some of the character of MGH Neuropathology is captured in an earlier account of the history of the Neuropathology Laboratory by E. P. Richardson Jr., published in *The News* at MGH in 1957 (1). The paragraph quoted below highlights both the complexity of the nervous system and the excitement of discovering its pathological processes, and thus serves as an appropriate introduction to this chapter:

> It may be wondered why it should be necessary to spend so much effort on the pathological examination of a single organ; yet it is quite apparent that the nervous system is itself made up of a large number of tissues, with interconnections of inconceivable complexity, and that a large number of areas must be examined in order to reach some idea as to the whole. Thus, the neuropathologist attempts, by the detailed microscopical study of the tissue sections, to gain some insights as to the presence of any disease process, and as to its nature. The cells and fibers that are disclosed by the microscope are dead, immobile structures; and yet, they are actors in a drama that are suddenly held still in the midst of their activity—in the midst of each pose or gesture—as in a photograph. It is the task of the tissue pathologist—and of the neuropathologist in this field of his activity—to infer, by means of his previous experience with other cases or with evidence of older or more recent stages of the disease process in the same case, what the scenes were that have gone on before, and what might have resulted had not the whole process terminated at that point. Viewed in this way, the scene may be that of a furious battle with hordes of cellular participants in various degrees of victory or defeat; or it may be more like a gradual, insidious decline and decay. Thus, in the mind's eye, the picture is no longer that of a dead stillness but, instead, of an active struggle between the forces of health and those of disease—the meaning of which may be readily apparent, or may yet defy interpretation. Or, it may be—as often is the case—that the florid manifestations observed during life are not reflected in any visible disturbances in the structures under scrutiny. This, too, must be discovered and understood. It must be admitted that there are disease processes which do not result in any

> changes that can be observed with the ordinary microscopical techniques at our disposal. Our methods are still inadequate to reveal subtle structural changes which must surely be present in many instances, and this must be an incentive to improve our techniques. Even then, it may well be that some cases of what could be called "disease" cannot be elucidated by any method of demonstrating structures, no matter how refined. This, too, we must know.

The history of neuropathology at MGH can be divided into four partially overlapping eras:

1. Before 1927, when a formal neuropathology unit was established. During this period surgical neuropathology was performed by the anatomical pathologists and research and autopsy neuropathology by the pathologists and neurologists
2. From 1927 until 1951, when the Neuropathology Clinical Service was managed largely by a single individual, Dr. Charles S. Kubik, and neuropathology research was collaborative with other individuals and departments, notably Dr. Stanley Cobb in Psychiatry
3. From 1951 through the late 1980s, during which Neuropathology was directed by Dr. Edward P. Richardson Jr. and dominated by the three "giants": Drs. Raymond D. Adams, C. Miller Fisher, and Richardson
4. From the late 1980s to the present day, when the Neuropathology group grew in terms of number of faculty and research resources, and during which time the directorship was transferred from Richardson to Dr. E. Tessa Hedley-Whyte and then to Dr. Matthew P. Frosch.

## The Early Days: Before 1927

In 1872 Dr. James Jackson Putnam was the first neurologist appointed to the MGH staff, and he founded the Neurology Department at Harvard Medical School (HMS). He had studied in Europe with both pathologists and neurologists, including Carl von Rokitansky, Theodor Meynert, and John Hughlings Jackson, and went on to become one of the founders of the American Neurological Association. While he was Chief of Neurology at MGH, he converted a portion of his home into a neuropathology laboratory. His primary interests were in clinicopathological correlations based on autopsy studies.

Dr. Edward Wyllys Taylor trained in neuropathology in Berlin with Hermann Oppenheim in 1891–1893. He returned to Boston as Assistant in Pathology at HMS in 1893. Influenced by Drs. J. J. Putnam at the MGH and W. N. Bullard at Boston City Hospital, Dr. William T. Councilman established a neuropathology laboratory for Taylor at HMS in 1902 (2). Dr. Taylor, while an Instructor in Neuropathology at HMS and a member of the Neurological Department of the MGH, published a classic paper on the pathological anatomy of poliomyelitis in 1902 (3). He argued that inflammation of the ventral horns caused motor neuron death rather than direct infection of the neurons themselves, and he made it clear that this was a controversial issue; nonetheless, it was agreed that the disease was due to an infectious agent. He wrote on a variety of neuropathological topics, including "Four Defective Brains" (4). Dr. Taylor succeeded Dr. Putnam as Chief of Neurology at MGH in 1906 and was later appointed the first James Jackson Putnam Professor of Neurology at HMS.

In 1912 Harvard University established the joint Department of Psychiatry, Neurology, and Neuropathology (5). By that time there was already a Bullard Professor of Neuropathology, Dr. Elmer Southard, the Bullard Foundation for Neuropathology at HMS having been established in 1906.

Dr. James Homer Wright (chapter 4), the Chief of Pathology from 1896 to 1926, wrote a number of papers on neuropathology. His report in the minutes of the Boston Society of the Medical Sciences in 1897 describing an "unusual degeneration of the spinal cord, in which there

was a well marked tract of ascending degeneration in one of the columns of Burdach," secondary to a metastatic breast cancer in the sacrum, demonstrated that he had a good knowledge of neuroanatomy (6). Dr. Wright followed this with a comprehensive monograph, with Dr. Councilman of HMS and Dr. Frank Burr Mallory of Boston City Hospital, on 111 cases of epidemic meningitides for the State Board of Health of Massachusetts in 1898 (7). Dr. Oscar Richardson (see chapter 3; no relation to E. P. Richardson Jr.), who was Dr. Wright's close associate for nearly 30 years, also contributed to the neuropathological literature, detailing a case of Friedreich's ataxia in 1898 (8).

Dr. Wright left another indelible mark on neuropathology, albeit indirectly. His seminal study of adrenal neuroblastoma, with its description of the characteristic rosettes that now bear his name, influenced the terminology used to describe other tumors showing similar neuronal differentiation, including primitive neuroectodermal tumors of the brain such as medulloblastomas (9). The term *Homer Wright rosette* has long been in common usage in neuropathology practice, far more so than the equivalent *Bailey's pseudorosette,* named after Percival Bailey, who described it in medulloblastoma.

The clinical chemistry laboratories of the Pathology Department also played a role in neuropathology. Analysis of the cerebrospinal fluid (CSF) was increasingly performed, the emphasis being on the detection of neurosyphilis. In 1922 the neurologist Dr. James B. Ayer, who had been working in the Pathology Department on a variety of projects of neuropathological interest, expanded the study of CSF to include certain routine examinations (total protein and colloidal gold) and other special tests (gum mastic and quantitative sugar). In 1922, 1,375 total protein, 908 colloidal gold, 374 gum mastic, and 228 quantitative sugar measurements on CSF were made. By 1924 the number of spinal fluids examined was 2,016. Dr. Ayer's close work with Pathology may have been one factor in the 1926 decision (once he was Chief of Neurology) with Dr. Tracy Mallory to establish a neuropathology laboratory that involved both the departments of Neurology and Pathology.

## Charles S. Kubik: The Early, Pre-MGH Years

Charles Soucek Kubik (figure 17.1) was born in Caldwell, Kansas, on February 4, 1891, and died in Lincoln, Massachusetts, on June 5, 1982, at the age of 91. He was one of six children and grew up on the family farm, where the family raised wheat and other crops and established peach, apple, and cherry orchards. As a youngster, he became adept at many chores on the farm, hunted, fished, and attended a nearby small country schoolhouse. He attended Caldwell High School, getting to

***Figure 17.1*** *Charles S. Kubik, Director of Neuropathology 1927–1951, mid-1930s*

school on horseback and staying with another family during the week because of the long distance from the farm; he graduated in 1908. He went on to receive his undergraduate degree from the University of Kansas in 1912 and his M.D. in 1916 from Rush Medical College in Chicago.

Dr. Kubik was accepted as an intern at Cook County Hospital in Chicago in 1916, but World War I intervened. He volunteered in the U.S. Army and served as Captain, Medical Corps, in the 131st Ambulance Company in the 33rd division in France, from 1917 to 1919. Following the war, he returned to Kansas to practice general medicine. In 1924 he decided to pursue training in neurology and psychiatry and went to the National Hospital for Nervous Diseases (now the National Hospital for Neurology and Neurosurgery) at Queen Square in London, which was at the time the preeminent center in the English-speaking world to train in neurology. Founded in 1859, it was the first hospital in Britain dedicated to the study of neurologic illness. There he also studied neuropathology under the stewardship of Dr. J. G. Greenfield, the author of what became the standard textbook in the field (10, 11). Indeed, Kubik was one of Greenfield's first fellows. Dr. Greenfield became a valued mentor, colleague, and friend, and when he visited Dr. Kubik at his home in Massachusetts in 1956, Dr. Kubik gathered his MGH Neuropathology and Neurology department colleagues to honor him.

After completion of his training in neurology and psychiatry, Dr. Kubik returned to America in 1926 and joined the Boston Psychopathic Hospital as a house officer in psychiatry. There he met his wife-to-be, Emily Knapp, a chemist working at the hospital. Soon thereafter, Dr. Kubik was invited by Drs. Ayer and Mallory to found a neuropathology laboratory at MGH.

## From 1927 to 1951: The Kubik Era

The special laboratory for Neuropathology in the Department of Pathology at MGH was established in 1927 under Dr. Kubik's leadership. At that time there were only about 10 established laboratories dedicated to the study of neuropathology and neurohistology in the world, notably at the National Hospital for Nervous Diseases in London; the laboratory of Jean-Martin Charcot and Charles Foix in Paris at the Salpêtrière (which had such students as Sigmund Freud, Joseph Babinski, William James, and Alfred Binet); distinguished centers in Breslau, Frankfurt, Munich, and Berlin (12); and the laboratory of Santiago Ramón y Cajal in Madrid, in which the seminal neurohistological studies were made that eventually led to Cajal's Nobel Prize.

From its inception, the MGH Neuropathology Laboratory had physicians from the departments of Neurology, Neurosurgery, Pathology, and Psychiatry in the laboratory participating in the study of cases. The original Neuropathology Laboratory was situated on the second floor of the Allen Street Building. Initially, Dr. Kubik had to borrow a microtome to cut tissue sections—until the day he stumbled across one (1): "Eventually, Dr. Kubik did obtain a microtome for the newly created laboratory. It happened that one day he chanced to notice, hidden away under the seats of the old Pathology Amphitheatre and heavily coated with the untouched dust of many years, an abandoned microtome, which further inspection showed him was still serviceable and of a type particularly suited for cutting neuropathological tissue sections. This was resurrected from its dusty repository and it performed usefully for years."

At first, Dr. Kubik cut and stained all his own sections, which were reportedly "beautifully cut and stained sections which remain as examples and inspiration for those who have followed him in this work" (1). Soon, however, as the service grew, Dr. Kubik recruited skilled technicians to help, initially Jean Engborg, who joined the laboratory in 1930 and who stayed a part of it through the late 1950s. Even after her retirement, Engborg continued to travel from Maine to the laboratory to perform silver impregnations on

frozen sections. The early group of technicians included Klara Edwards, the Chief Technician in Neuropathology from the late 1940s until finally retiring in 1979, whom E. P. Richardson noted for her "ceaseless interest and conscientious work of the highest quality" (1). Olgerts Zvaigzne, who worked primarily in Dr. Adams's Experimental Neuropathology Laboratory, was an expert in celloidin embedding and prepared whole brain sections for the clinical laboratory.

Kubik was responsible for all the clinical neuropathology, in addition to a neurology practice, until 1949 when he was joined by Dr. E. P. Richardson Jr. Dr. Kubik was known for his detailed approach to neuropathological materials, although he appeared to favor autopsy neuropathology over surgical neuropathology. Looking over his surgical pathology reports, one is impressed by their brevity, and the pathologists used to complain about the time it took him to sign out the more complicated biopsies (13). His careful approach was also ideal for training and Dr. Kubik trained a number of future leaders in neuropathology, most notably Drs. Raymond Adams and E. P. Richardson.

In 1946, Dr. Kubik initiated the Tuesday afternoon Neuropathology Brain Cutting Conference at the MGH. In this conference a case known to the clinical staff that had come to postmortem examination was first presented in clinical detail and then discussed by the attendees, beginning with the medical students and proceeding to the most expert clinicians. The fixed brain was then cut and the findings analyzed in the context of the clinical picture. The remarkable utility of this exercise is that it allows all attendees, from the neophyte to the expert, to attempt to localize the lesion anatomically on the basis of clinical signs and symptoms and generate a differential diagnosis as to the pathologic basis of the clinical disease. This exceptional conference continues to the present day as an essential component of the MGH Neuropathology teaching program. For the past three years it has been conducted in the early hours of Friday morning—and seen a satisfying increase in attendance.

***Figure 17.2*** *In the Ether Dome, ca. 1960. Standing, left to right: Benjamin Castleman, Charles Kubik, Raymond Adams. Seated, second row: Robert Schwab, C. Miller Fisher, Philip Dodge, Ernest Picard. Seated, third row: Maurice Victor, Shyam Pant (probable), P. M. Dalal.*

A second important conference to which Dr. Kubik and Neuropathology contributed was the weekly Clinicopathological Conferences (CPCs), held on Thursdays in the historic Ether Dome (figure 17.2). When the case to be presented was of neurologic interest, Dr. Kubik participated either as the neurologist who discussed the differential diagnosis or as the neuropathologist who demonstrated the findings. He was known for being careful with his words and, as such, was a superb teacher. The extraordinary care in the workup of these cases and the quality of the discussion at these conferences is well illustrated in *Neurological Clinicopathological Conferences,* by E. P. Richardson and Benjamin Castleman (14).

Dr. Kubik held various appointments at

Harvard Medical School, rising through the ranks to Associate Clinical Professor of Neurology. He was not a prolific writer, but his careful approach to neuropathology contributed to a series of important papers during his tenure, including the classic clinicopathological study of basilar artery occlusion that is still cited (15) and the description of the lateral medullary infarct (16). Dr. Kubik with Dr. Adams assembled an encyclopedic compendium of the pathology of demyelinating diseases (17). This last publication is notable for providing a classification of this group of diseases and defining them by their preferential attack on myelin and myelin-forming cells. Additionally, like Taylor's earlier paper, it provides outstanding clinical and pathological correlation (18). Other topics included a method of removal of iodized compounds from the CSF (19) and infections of the nervous system (20).

In addition to directing the Neuropathology Laboratory at the MGH, Dr. Kubik was active on the Neurology Service as a consultant attending physician. Dr. Adams, who was a junior resident at the MGH when he first met Kubik in 1938, said that Dr. Kubik had "one of the most astute minds in Neurology at the time" (13). Dr. Kubik also served as Chief of Neurology at the MGH from 1946 to 1951, after Dr. Ayer retired as chief.

Dr. Stanley Cobb, the Chief of Psychiatry at the MGH from 1934 to 1955, was a major collaborator with Neuropathology during the Kubik era. Born in 1887, Cobb graduated from Harvard College in 1910 and HMS in 1914. After a surgical internship at Peter Bent Brigham Hospital with Dr. Harvey Cushing, he studied physiology for a year with Dr. William H. Howell and psychiatry for two years with Dr. Adolph Meyer, both at Johns Hopkins University. Following Army service in World War I, he worked for four years at MGH, followed by a two-year Rockefeller Fellowship, which allowed him to study Neurology at Queen Square, as well as with Jean Lhermitte in Paris, Cécile and Oskar Vogt in Berlin, and Sir Charles Sherrington at Oxford. He was called back to Harvard as Bullard Professor of Neuropathology and Director of the new Neurological Unit at Boston City Hospital. There he continued his studies of neuropathology and neuroanatomy (21) until he was recruited, in 1934, to be the Chief of the first Psychiatry Service at MGH—and to create the department. After he retired as chief, Dr. Cobb returned to his long-term interest in ornithology and comparative avian neuroanatomy, collecting and studying the brains of different species of birds under the microscope. He remains well known for his many contributions to the field of psychiatry and for his later interest in the environment, including a piece entitled "Death of a Salt Pond," published in the *Cape Cod Times* during his retirement. He died in 1968.

## Charles S. Kubik: The Later Years

Dr. Kubik retired from his administrative duties in 1951. Dr. Adams succeeded him as Chief of Neurology, and Dr. E. P. Richardson Jr. took over the direct supervision of the Neuropathology Laboratory at the MGH. Dr. Kubik remained on the staff as Senior Consultant in Neurology and Neuropathology, regularly working in the laboratory and pursuing his work in clinical neurology for the next 20 years or so. In 1974 a tribute to Drs. Kubik and Richardson was held on the occasion of the overlapping meetings of the American Association of Neuropathologists (AANP) (Dr. Richardson was President of the AANP that year) and the American Neurological Association (ANA) in Boston. This was possibly the last time that the ANA and the AANP met together. More than 140 alumni of the MGH Neuropathology Laboratory attended this festive occasion. The residents were particularly fond of recalling the yearly excursions to the Kubik home in Lincoln; they were invited to leave the ward to go apple picking! Throughout his long life, Dr. Kubik was known to maintain a close focus on whatever task was at hand; for example, in his eighties, he was said to have easily regained

composure after falling from a ladder positioned precariously against a tree whose damaged limb required hand-sawing.

## From the 1950s to the 1980s: The Era of Richardson, Adams, and Fisher

Neuropathology remained, along with most of the rest of the anatomic pathology laboratories, in the Allen Street Building until the opening of the Warren Building in 1956. In 1957 the Neuropathology Laboratory and the offices moved onto the second floor of the Warren Building, where they would remain through 1977.

As mentioned above, Dr. Raymond Adams became Chief of the Neurology Service at MGH in 1951 (figures 17.2, 17.3, and 17.4). Dr. Adams was a remarkable individual who is considered the most influential academic neurologist of the second half of the twentieth century (13). He was a native of Oregon and graduated from the new Duke University Medical School in 1936. Following a Rockefeller Fellowship to study neurology at the MGH and psychiatry at Yale, he moved to Boston City Hospital to train in neurology and work with Dr. Derek Denny-Brown. It was during his tenure at Boston City Hospital that his interest in neuropathology began and flourished. Dr. Adams considered himself as much a neuropathologist as a neurologist, and the authors recall sitting with him reviewing microscopic specimens when he was well into his eighties. His emphasis on the neuropathological basis of neurological disease was also imprinted on all of his many trainees over the decades, to the extent that all MGH Neurology residents spent a full year of their three residency years studying neuropathology. His many contributions to the fields were based to a large extent on his combination of clinical and neuropathological expertise. The breadth of his interests in neuropathology was wide, extending from muscle disease (22, 23) to peripheral nerve disease (24) to neurodevelopmental disorders, demyelinating conditions (17), neoplasms (25), and metabolic diseases (26). He was the author of many books, including two textbooks on neuropathology (27, 28). Dr. Adams died in 2008, aged 98.

During his tenure as Chief of Neurology from 1951 to 1977, Dr. Adams took MGH Neurology from a small clinical department to a large, partly subspecialized department involved in extensive research activities. One of Dr. Adams's key recruits in his early days was Dr. C. Miller Fisher, who joined the MGH Neurology Staff in 1954 (figure 17.3). Dr. Fisher was born in 1913 and grew up in Manitoba. He graduated from the University of Toronto Medical School in 1938. After internship and a year of residency in medicine, he joined the Royal Canadian Navy in World War II. His ship was torpedoed in the Atlantic, and he spent the rest of the war as a prisoner in Germany (1940–1945). After the war,

***Figure 17.3*** *E. P. Richardson (foreground), Miller Fisher, and Raymond Adams (standing) poring over a brain in the Warren basement, ca. 1976*

***Figure 17.4*** *Neuropathology, 1968–1969. Front row, left to right: Eileen Ouellette, Margaret Norman, Raymond Adams, Charles Kubik, E. P. Richardson, Elizabeth Dooling. Second row: Karl Åström, Richard Baringer, Donald Price, Horatio Aldredge, William Schoene. Third row: Surl Nielsen, Edward Wolpow, Fred Cantor, Walter Bradley, Henry Schmidek, Robert Ackerman.*

he returned to Montreal as a Fellow in Neurology at the Montreal Neurological Institute, spending much of his time in neuropathology. He then spent a year as a fellow at Harvard before returning to the Montreal Neurological Institute as Neuropathologist and Lecturer in Neurology for four years. He was appointed Neurologist and Associate Neuropathologist at MGH in 1954 and Consultant in Neuropathology in 1984, resigning in 2005, when he was over 90. His tenure was characterized by his astounding attention to detail and his near-total recall, which seemed to involve every patient and every brain he had ever examined. He was renowned for his lack of interest in time (manifested by his never wearing a watch after his wartime experiences), his late nights and weekends examining patients in extraordinary detail, and his interest in "serial sections" of histological material, notably blood vessels. Well into his eighties, he would come to the weekly Neuropathology Brain-Cutting Conferences, weigh the clinical details carefully, point out the lack of primary description of the clinical signs, opine at length on the likely diagnosis (nearly always arriving at the correct one), and then make suggestions on how further careful analysis of the patient's clinical history and signs and more detailed examination of the brain (usually with serial sections!) might yield unique insights on the case. These skills made Dr. Fisher

a pioneer in careful clinicopathological correlation in the field of neurovascular diseases, and his work is considered by many to have heralded the modern era of understanding stroke (16, 29).

Dr. E. P. Richardson Jr., known universally as "E.P.," rejoined the Neuropathology Laboratory in 1949, after a sojourn at Queen Square with J. G. Greenfield, took over its direction from Dr. Kubik in 1951, and remained the primary neuropathologist at MGH through the 1980s and a faculty member in Neuropathology until his death in 1998 (figures 17.3 through 17.6). Originally trained in neurology and psychiatry, he continued a limited clinical practice in neurology, which included attending on the wards for a month each year until 1982. Dr. Richardson, like Drs. Adams and Fisher, was gifted in his abilities to correlate the clinical and neuropathological details of neurological disease. His dominant role as the neuropathologist at MGH during the rapid expansion of the Neurology Service and its training programs provided him an unparalleled opportunity to work with some of the brightest young academic neurologists of his time. His patience in teaching, long remembered by all who trained with him, made him an ideal educator. As the quote at the start of this chapter demonstrates, Dr. Richardson was excited by the study of neuropathological processes. His contributions to the field are extensive and wide-ranging and are discussed in chapter 11.

Dr. Richardson ran the clinical service for

***Figure 17.5*** *Neuropathology, 1985. Front row, left to right: Neil Kowall, E. P. Richardson, Cecil Treip, Tessa Hedley-Whyte, Raymond Sobel. Second row: Dana Gabuzda, Dora Hsu (technologist), Robert Ferrante (chief technologist), Susan Smith (secretary), Lu Ning Wang (research fellow). Back row: Suzanne de la Monte, Bruce Hamaty (technologist), Margie Hodges (secretary), Holly Goolsby (technologist).*

***Figure 17.6*** *E. P. Richardson's eightieth birthday celebration, 1998. Left to right: Umberto De Girolami, Margie Hodges (secretary), Jean Paul Vonsattel, Kettelie Allien (secretary), Kathy Newell, Peggy Richardson, Robert Colvin, E. P. Richardson, Maria Ullian (technologist), Tessa Hedley-Whyte, Suzanne de la Monte, Holly Goolsby (technologist), Dora Hsu (technologist), Matthew Frosch, David Louis.*

many decades, with help primarily from the trainees. Dr. Karl Erik Åström worked closely with Dr. Richardson as a member of the service from 1966 to 1979 (30) (figure 17.4). Dr. George M. Kleinman, a graduate of the program, was Assistant Neuropathologist from 1977 to 1981, during which time he participated in the Childhood Brain Tumor Consortium (see below). Dr. Kleinman later joined the faculties at New York University and then Mount Sinai School of Medicine.

Neuropathology was busy during this period: the number of surgical neuropathology specimens increased, from 139 neurosurgicals (including 32 muscle biopsies and 11 nerve biopsies) in 1956 to 204 (including 49 muscle and 43 nerve) in 1966, and there were approximately 500 autopsies per year. The types of case material examined in the laboratory varied during this period. Review of the autopsy volumes shows the polio epidemic of the 1950s, and the experience with developmental disorders from 1956 to 1980, when the laboratory was responsible for the autopsies on the decedents at the Wrentham, Paul A. Dever, and Walter E. Fernald state schools. In the 1950s and 1960s many cases were sent to Dr. Paul Yakovlev in the Warren Museum at HMS for whole brain embedding in celloidin and serial sectioning, and many of Dr. Yakovlev's sections still reside on Warren 3.

During this time, Neuropathology was actively supported by Dr. Benjamin Castleman, who

served as the Chief of the Pathology Service from 1952 through 1974. Nonetheless, Neuropathology was considered quite distinct from the rest of Pathology, and Anna Castleman was surprised, upon meeting David Louis in 2009, to hear that a "neurologist" had been appointed Chief of Pathology in 2006.

Dr. Raymond Adams established the separate Experimental Neuropathology Laboratory as part of the Neurology department, under his and Dr. Fisher's direction. This laboratory was originally on the fourth floor of the Bulfinch Building, later moving to the seventh floor of the Vincent Burnham Kennedy Building. This was the initial supporting laboratory for the Brain Bank in the early days of the Massachusetts Alzheimer's Disease Research Center (MADRC), in the mid-1980s.

## From the 1980s to the Present Day

Dr. E. Tessa Hedley-Whyte was recruited to MGH Pathology from New England Deaconess Hospital in 1981 (figure 17.7). She was born in London, England, in 1937, grew up in Newcastle-upon-Tyne, and graduated from the University of Durham Medical School, in Newcastle-upon-Tyne, in 1960. She began a pathology internship in 1960 at Boston's Children's Hospital under the tutelage of Drs. Sidney Farber and Gordon Vawter, followed by a year each at New England Deaconess and Peter Bent Brigham hospitals with Drs. William A. Meissner and Gustave Dammin. After six months of training in neuropathology at Children's Hospital with Dr. Floyd H. Gilles and six months of fetal and obstetric pathology with Drs. John Craig and Shirley Driscoll, Dr. Hedley-Whyte became a research fellow with Dr. Betty Geren Uzman, an early pioneer of applied electron microscopy and the study of myelination of peripheral nerve at the Children's Cancer Research Foundation. Dr. Hedley-Whyte was recruited to the staff of Children's Hospital to develop the Electron Microscopy Unit and establish a research program for the Mental Retardation Center in 1967. During the next 10 years she

***Figure 17.7*** *E. Tessa Hedley-Whyte, Director of Neuropathology, 1989–2007, in 2007.*

was also a part-time neuropathologist at both Peter Bent Brigham (1968–1971) and Beth Israel hospitals (1971–1977), as well as consultant to New England Deaconess Hospital. In 1977 Dr. Hedley-Whyte joined the Pathology staff at New England Deaconess and Baptist hospitals as an anatomic and neuropathologist and then moved to the MGH in 1981 (31). Dr. Hedley-Whyte was named head of Neuropathology in 1988, becoming the third director of the Neuropathology Laboratory at MGH and the first pathologist-neuropathologist to hold this post. This change coincided with a national shift in the numbers of neuropathologists who were originally trained as neurologists to those originally trained as pathologists. As a result, nearly every faculty neuropathologist appointed after 1981 has been a pathologist-neuropathologist (with the exception of Dr. Ann McKee; see below). This trend coincided

with a gradual decrease in the amount of time spent by neurology residents in neuropathology training, from the one full year under Dr. Adams progressively down to the current two months.

Dr. Hedley-Whyte's interests, like Dr. Richardson's, have been broad within the field of neuropathology, and her specific emphases are on myelin formation, blood-brain barrier alterations, prognostic factors in brain and pituitary tumors, and neurodegenerative diseases (32–39)—many of these studies in collaboration with her longtime research assistant, Dora Hsu, M.Sc. Dr. Hedley-Whyte's contributions to the teaching programs, as Training Program Director for both Pathology (1985–1996) and Neuropathology (1988–2007), have been exemplary, as have been her talents as an astute observer and her extraordinary devotion to the teaching of neurology and pathology residents as well as neuropathology fellows (figures 17.5, 17.6, and 17.8). Three of her fellows have become chairs of academic pathology departments and one has been a Dean. Dr. Hedley-Whyte's many national activities include 12 years of service as Moderator of the Annual Diagnostic Slide Session of the AANP.

Other primary clinical faculty and their research interests during this time included George Kleinman (1977–1981, brain tumors); Raymond A. Sobel (1982–1992, demyelinating diseases); Jean Paul Vonsattel (1988–2001, Huntington's disease and brain banking); Suzanne de la Monte (1987–1999, AIDS and Alzheimer's disease); Ann McKee (1991–1994, neurodegenerative diseases); David N. Louis (1991–present, brain tumors); Matthew P. Frosch (1994–present, neurodegenerative diseases); Anat O. Stemmer-Rachamimov (2002–present, hereditary brain tumor syndromes); Di Tian (2009–present, autism). Faculty appointed on a consultative or temporary basis has included Drs. Hannah Kinney (1982–1992) and Matthew Anderson (1999–2002).

This period witnessed many changes in location and affiliation of different components and personnel. The Neuropathology offices and laboratory moved up one floor in 1977 to the third floor of the Warren Building, where the offices have remained to the present day. That location put Neuropathology next to the Neurology and Neurosurgery research laboratories (Drs. Shirley Wray, Adelbert Ames III, Robert H. Brown Jr., Stephen Hauser, Marian DiFiglia, among others) and the Neurology Electron Microscopy (EM) Unit. The EM unit had been established by Humberto Fernandez-Moran (biophysicist in Neurosurgery at MGH, 1959–1962). This unit was later directed by Dr. Harry deF. Webster, and subsequently by Drs. Dennis Landis and John Halperin; it undertook the ultrastructural analysis of all nerve, muscle, and brain biopsies. In the early 1980s, when Dr. Landis left, the Zeiss-9 electron microscope and technician (Holly Goolsby) were transferred to Neuropathology. In 1993 the ultrastructural examination of neuropathological specimens was combined with the rest of diagnostic electron microscopy in the Pathology Department EM unit on Cox 5. In 1998 the Neurohistology Lab was closed down after 70 years and its responsibilities merged into the new departmental Histology Laboratory on Blake 3. And in 1999 Dr. Hedley-Whyte's research laboratory on Warren 3 closed, and Warren 3 was remodeled again to accommodate the Clinical Electron Microscopy Unit, which moved from Cox 5 to Warren 3 in 2000.

Surgical neuropathology practice grew during this time, while the number of autopsy brains decreased, in parallel with national trends. For example, yearly neurosurgical specimens were approximately 700 in 1981 but had risen to 1,029 by 2009. On the other hand, postmortems with brain examination numbered 400 in 1980 but only 187 in 2009; and nerve and muscle biopsies totaled about 360 in 1980 but had dropped to 156 in 2009. The sequential numbering of the autopsies (begun in 1896) came to an end at 46,054 with the introduction of a new anatomic pathology laboratory information system, CoPath, in 1990. In 2004, with the change to another system

(PowerPath), the neuropathological part of each autopsy was given a separate accession number.

The increase in neurosurgical specimens was accompanied by a growth in the neuro-oncology practice at MGH. An informal neuro-oncology conference had been established in the mid-1980s by Drs. Rita Linggood of Radiation Oncology, Robert Ojemann and Paul Chapman of Neurosurgery, and Dr. Hedley-Whyte of Neuropathology. A formal adult brain tumor management conference was established with the foundation of the Brain Tumor Center at MGH in the early 1990s. A pediatric brain tumor conference was established when Dr. Nancy Tarbell became Chief of Pediatric Radiation Oncology in 1997; the emphasis was on whether children would derive particular benefit from proton beam as opposed to conventional radiotherapy. The neuropathologists have maintained a strong presence at both of these important clinical management conferences, and the Neuropathology fellows play a key role in presenting and discussing biopsy findings.

The period also saw an increase in the amount of grant-funded research activities in Neuropathology, focused primarily on neurodegenerative diseases and on brain tumors. Dr. Hedley-Whyte was a coinvestigator of the Childhood Brain Tumor Consortium (Dr. Floyd Gilles, Children's Hospital Boston, was the principal investigator). Drs Richardson, Hedley-Whyte, Sobel, and Kleinman of the MGH were "slide readers" in this project, reading slides from more than 3,000 pediatric brain tumors from five North American institutions (37–39). The MADRC was established in 1984, Dr. John Growdon of Neurology serving as the principal investigator. A compulsory condition of this grant was the establishment of a neuropathology core, including a brain bank. Dr. Hedley-Whyte was the principal investigator of this core from its start in 1984 until 2007. Importantly, the core included funds for a Neuropathology fellow. The first fellow was Dr. Suzanne de la Monte, who set up the management systems for these studies, which are still in use today. The Brain Bank was initially a freezer in Dr. Growdon's laboratory, and staffed by Olgerts Zvaigzne, a histotechnologist in the Experimental Neuropathology Laboratory; both labs were on Burnham Kennedy 7. A small laboratory on an upper floor of the Warren Building, with its own histotechnologist, was acquired for histology about 1987; around 1991 the lab moved to larger quarters on Burnham 8. When Dr. Jean Paul Vonsattel became codirector of the MADRC Brain Bank in 1996, he was able to improve its procedures significantly using his experience with the Brain Tissue Resource Center at McLean Hospital (40). With the opening of the Neuroscience Center in Building 149 in 1991, Dr. Vonsattel became Director of the Molecular Neuropathology Laboratory and the Associate Director of the Brain Tissue Resource Center at McLean, where he was able to continue his research into Huntington's disease and develop his brain banking procedures. When the Center for the Study of Neurodegenerative Diseases moved into the newly renovated Building 114, the MADRC Brain Bank moved from Burnham 8 to the third floor of Building 114, where it had two dedicated rooms, one for dissection and one for histology, as well as an office for the database manager–histologist (Karlotta Fitch since 1991) and an office for Dr. Vonsattel. The fellowship funding from the MADRC has proven important for the training program: of a total of 20 MADRC Neuropathology fellows to date, seven are involved in research of neurodegenerative disorders and 16 are in academic neuropathology.

Dr. Raymond A. Sobel arrived at the MGH in 1981 as a research fellow in immunology with Drs. Robert Colvin and Robert McCluskey, having completed neuropathology training at Stanford University Medical School with Dr. Lucien Rubinstein (figures 17.5 and 17.8). He joined the faculty in 1982 and had an active research program exploring the mechanisms of demyelinating diseases (41–44). He returned to Stanford in 1992 to continue his work on neuroimmunology

and multiple sclerosis, becoming Professor of Pathology and then Editor of the *Journal of Neuropathology and Experimental Neurology.*

Jean Paul Vonsattel, a graduate of the University of Lausanne, came to the MGH as a research fellow with Dr. Richardson in 1981 and was assigned to the Brain Bank of the new Huntington's Disease Center without Walls at McLean Hospital (figures 17.6 and 17.8). He later became a clinical fellow and resident in anatomic pathology before joining the faculty in 1988. His grading of the neuropathological changes in Huntington's disease brains has been significant in the study of this condition (45, 46). He also had a long-standing interest in amyloid angiopathy (47). Dr. Vonsattel became Professor of Neuropathology and Director of the New York Brain Bank at Columbia University in 2001.

Dr. Suzanne de la Monte commenced her neuropathology training with Dr. Richardson in

***Figure 17.8*** *Celebration in honor of E. Tessa Hedley-Whyte, with her colleagues and trainees in front of the Bulfinch Building, November 2007. Front row, left to right: Leroy Sharer, David Louis, Joseph B. Martin, Tessa Hedley-Whyte, John Hedley-Whyte, Matthew Frosch, John M. (Jack) Lee. Second row: Kathy Newell, Joe Ma, Raymond Sobel, Shirley Wray, Anat Stemmer-Rachamimov, Hannah Kinney, Douglas Miller, Rolf Pfannl, Robert Colvin, Jeffrey Golden. Third row: Stefanie Freeman, Karlotta Fitch, John Henson, Alyssa Lebel, Verne Caviness, Elizabeth Engle, Ann McKee, Jonathan Horton. Fourth row: Pavan Auluck, Krishan Krishnamurthy, Hart Lidov, Je Eun Kim, Elizabeth Lee-Lewandrowski, Ivana Delalle, Nancy Harris, David Cardozo, Rebecca Folkerth, Suzanne Mirra. Fifth row: Di Tian, Michael Lawlor, Pornsook (Mint) Cheonchun, Lester Adelman, Bradley Hyman. Sixth row: Christopher William, Matija Snuderl, Thor Stein, Elizabeth Dooling, Holly Goolsby, Jean Paul Vonsattel, Robert Brown.*

***Figure 17.9*** *MGH Neuropathology faculty, 2010. Left to right: Tessa Hedley-Whyte, Di Tian (standing), Matthew Frosch (Director of Neuropathology 2007–), Anat Stemmer-Rachamimov (standing), David Louis.*

1984 and joined the faculty in 1987 (figures 17.5, 17.6). Dr. de la Monte's research included investigations into neurodegenerative diseases; she was involved in setting up the MADRC Brain Bank databases. She has also investigated the effects of AIDS on the brain (48–50). She became Professor of Pathology, Medicine and Neuroscience at Brown University in 1999.

Dr. David N. Louis (chapter 25) completed his training in Anatomic and Neuropathology at the MGH in 1991, and in 1992 he took over the Molecular Neuro-Oncology Laboratory (figures 17.6, 17.8, and 17.9). Dr. Louis's work in brain tumors grew out of the seminal studies done by Dr. James Gusella and his fellow, Dr. Bernd Seizinger, in linking genes responsible for hereditary brain tumor syndromes, such as the neurofibromatoses. Dr. Louis went on to demonstrate the utility of molecular genetic approaches in subdividing malignant gliomas into clinically relevant entities. He showed that the loss of chromosomes 1p and 19q in anaplastic oligodendrogliomas was associated with a better overall survival and predicted a better response to chemotherapy. His important contributions to our understanding of the role of molecular alterations in the genesis and behavior of gliomas have been recognized by his numerous awards and his invitations to author and edit the World Health Organization classification of brain tumors as well as *Greenfield's Neuropathology* and other neuropathology references (11, 51–53).

Dr. Matthew P. Frosch, after completing his training at Brigham and Women's Hospital, joined the MGH faculty part-time in 1994 and full-time in 2002 (figures 17.6, 17.8, and 17.9).

His particular interests have been in neurodegenerative disease and amyloid angiopathy, including animal models of these diseases (54–56). Frosch attended Amherst College and HMS, graduating with an M.D. and Ph.D. from the combined Harvard and MIT Health Sciences and Technology (HST) program in 1987. Dr. Frosch is the Lawrence J. Henderson Associate Professor of Pathology and HST at MIT and is responsible for the teaching of neuroanatomy to the HST students. Since 2008 he has run the admissions process for the HST program. In addition, he is the faculty coordinator for the tissue-based activities of the Harvard NeuroDiscovery Center.

Dr. Anat Stemmer-Rachamimov was born in Israel, lived in Iran, and obtained her medical degree from the University of Milan in 1982 (figures 17.8, 17.9). She received her training in pathology at the University of Newfoundland and in neuropathology in London, Ontario, before joining David Louis as a research fellow in tumor genetics in 1997. She joined the MGH faculty in 2001 and became Associate Director of Ophthalmic Pathology in 2008. Her research area is the molecular and genetic biology of Schwann cells, neurofibromatosis, schwannomatosis and analysis of animal models of these diseases and other inherited tumor syndromes (57, 58).

Dr. Di Tian was born in China and obtained his medical degree from Beijing Medical College in 1992 and his Ph.D. from Northwestern University in 1998 (figures 17.8 and 17.9). After completing anatomic and neuropathology training at the MGH, he joined the faculty in 2009. His research area is the cellular and molecular origins of autism.

A major administrative change took place in 2006, when David Louis became the sixth Chief of the Pathology Service—the first neuropathologist to occupy the position. And, in 2007, Matthew Frosch succeeded Tessa Hedley-Whyte as Director of Neuropathology. In November of that same year, a gathering of Dr. Hedley-Whyte's current and former trainees and colleagues celebrated her contributions at MGH (figure 17.8).

## Educational Activities

MGH Neuropathology has always been involved in extensive educational activities involving medical students, residents, fellows, and practicing physicians. In particular, the residency and fellowship programs have trained hundreds of neuropathologists, neurologists, pathologists, and neurosurgeons, and more than 200 trainees have spent extended periods in the division. All together, the training program has produced approximately 50 practicing neuropathologists, in addition to many part-time neuropathologists and a number of chairs of neurology and pathology departments.

Depending on which source you believe, the first recognized trainee in neuropathology at MGH was either Walter Igersheimer in 1944, in the newly established position of Research Fellow in Neuropathology (according to Tracy Mallory's 1944 annual report), or Dr. Mary Lorraine Gannon in 1947 (according to E. P. Richardson [1] and Nathaniel Faxon [59]; however, the first mention of Gannon in the bound autopsy volumes is as a resident in Neuropathology in 1949). One of the autopsy volumes for 1949 also lists a fellow in Neuropathology, Dr. Rafael Estrada from Cuba. Another early mention of a neuropathology trainee in the autopsy volumes is in September 1951: Dr. Lysia Saxe (later Forno) is listed as clinical fellow in Neuropathology, and Dr. Remedios (Rose) Rosales is listed as Neuropathology resident. Some of the early trainees became full-time neuropathologists; in addition to Lysia Forno and Remedios Rosales, these include Lowell Lapham, Françoise Robert, Harry Webster, George Collins, and Betty Q. Banker.

In the 1950s and early 1960s most trainees came from Neurology and Psychiatry and all the Neurology residents spent at least one full year in Neuropathology. In 1967 the first pathologist was accepted for training with Dr. Richardson,

Virgilio Sangalang from Halifax, Nova Scotia. Many of the residents were supported by a training grant in neuropathology administered by Drs. Adams and Richardson, including individuals who went on to successful academic careers in neuropathology, such as Drs. Arthur Asbury, Byron Kakulas, Donald Price, Virgilio Sangalang, William Schoene, Surl Nielsen, Colin Masters, Margaret Norman, Herbert Schaumburg, Umberto De Girolami, Peter Johnson, Henry Powell, and John Trojanowski. After Dr. Joseph B. Martin succeeded Dr. Adams as Chief of Neurology in 1978, the neurology residents' experience in Neuropathology was decreased to six months; later, as the number of residents in the neurology training program increased, it was further reduced to four months and, in 1999, to two months.

Although the MGH had long had a robust training program in neuropathology, the Accreditation Council for Graduate Medical Education (ACGME) did not begin separate accreditation of neuropathology training programs until 1971. Dr. George Kleinman commenced the paperwork for formal accreditation of the MGH program in 1980, and Dr. Hedley-Whyte completed the application with Dr. Richardson as the Program Director and Dr. Hedley-Whyte as codirector. Accreditation was granted in 1982 for two trainees per year in a two-year program, although hospital funding was available for only one trainee per year. Dr. Douglas C. Miller was the first trainee in the officially accredited program. Beginning in 1990, the program began to accept a new resident each year instead of every other year, funding coming the second year through the MADRC. This enabled trainees to undertake more in-depth research projects as well as to gain broad experience of the neurodegenerative disorders. In 1995 Dr. Richardson and his wife established the E. P. Richardson, Jr. Fellowship in Neuropathology, which has enabled fellows to pursue additional years of research following their residencies; Dr. Kathy Newell was the first fellow. Currently the program is accredited for three trainees per year, and since 1982 the program has graduated 23 board-certified neuropathologists, all but two of them now practicing full-time neuropathology.

In 1995 a two-month exchange of neuropathology fellows was arranged between Children's Hospital/Brigham and Women's Hospital Neuropathology and the MGH Neuropathology training programs so that the MGH fellows could gain additional experience with fetal and pediatric pathology, and the Children's Hospital/Brigham and Women's Hospital residents could study material from the MADRC. In 2010 this rotation was reduced to one month, as the fetal and neonatal experience at MGH had been greatly augmented by the return of an obstetrical service in 1999. Experience in forensic neuropathology had been gained at MGH itself until the mid-1980s, as all trauma and burns deaths at MGH were autopsied at the hospital on behalf of the Medical Examiner. After that time, the Medical Examiner took cases to the office near Boston City Hospital, where the brains were cut by Dr. Thomas Kemper, and the neuropathology fellows had to go to Boston City to participate in these brain cuttings. Dr. Hedley-Whyte became a consultant to the Medical Examiner in 2007 and takes the fellows twice a month to learn forensic neuropathology.

One of the traditions of the teaching program that has existed since Charles Kubik's time is the weekly evening Mystery Case Conference. According to E. P. Richardson, this was instituted while he was a trainee as a dedicated time for the residents to spend with Dr. Kubik when he would not be seeing patients. This conference was later directed by Dr. Adams and Dr. Richardson, and attended by Dr. Fisher and all the neurology trainees on rotation in Neuropathology. This session was sufficiently highly regarded in the 1960s that Dr. Floyd Gilles from Children's Hospital, Boston, was also a regular attendee. It continues in a robust manner to the present day, although it no longer includes the traditional

supper and gossip in the cafeteria before viewing the slides.

The program has also participated in HMS courses for many decades. From at least 1956 until the late 1960s, MGH Neuropathology trainees attended the evening course in neuroanatomy, neurophysiology, and pathology of the nervous system directed by Dr. Paul Yakovlev and later by Drs. Richard L. Sidman and Merrill K. Wolf at HMS. Moreover, the Neuropathology trainees and faculty have also played a strong role in the teaching of neuroanatomy and neuropathology at HMS. Dr. Stanley Cobb, Chief of Psychiatry at the MGH, was responsible for the medical student teaching of neuroanatomy and neuropathology, followed by Dr. Adams. Drs. Adams, Alfred Pope, and Richardson conducted a six-week course in neuropathology for HMS students from the 1950s until 1968, which was well received by the Neuropathology trainees (13, 27). This course was offered for the next few years as an advanced one-month elective neuropathology course by Drs. Richardson and Pope. Dr. Richardson was an active participant in the design of the "Human Nervous System and Behavior" course in the HMS New Pathway program in the late 1970s; this course was redesigned in 1987 with the help of Drs. Richardson and Hedley-Whyte. All members of the staff and trainees continue to teach in the neurosciences in both the standard HMS and the HST programs. David Louis was the HST Neuroanatomy Course Director from 1994 to 2001 and was succeeded by Matthew Frosch, who continues in this role.

Other educational activities of the MGH Neuropathology group have included extensive participation in the MGH Case Records (chapter 24). For example, members of the group were the pathologist discussants in approximately 100 CPCs between 1981 and 2010. The group has also edited or written a number of major textbooks, including *Pathology of Peripheral Nerve* by Drs. Richardson and De Girolami (60), the eighth edition of *Greenfield's Neuropathology,* edited by Drs. S. Love, Louis, and D. Ellison (11), the 2007 *World Health Organization Classification of Tumours of the Central Nervous System,* edited by Drs. Louis, H. Ohgaki, O. Wiestler, and W. Cavenee (52), and the Armed Forces Institute of Pathology fascicle *Non-Neoplastic Diseases of the Central Nervous System* by Drs. Louis, Frosch, H. Mena, E. Rushing, and A. Judkins (61). Drs. Frosch and De Girolami have also authored multiple editions of the nervous system chapter in *Robbins and Cotran Pathological Basis of Disease,* and Drs. Louis, Frosch, Hedley-Whyte, and Sobel contributed chapters to the 2004 edition of *Escourolle and Poirier's Manual of Basic Neuropathology* (edited by F. Gray, U. De Girolami, and J. Poirier) (62).

## National Leadership

The successes of MGH Neuropathology over the years have also been demonstrated by national leadership in the field. For example, Drs. Adams (1955), Richardson (1974), Hedley-Whyte (1996), and Louis (2010) all served as President of the American Association of Neuropathologists, and Drs. Adams (1979), Richardson (1988), and Hedley-Whyte (2005) each received the American Association of Neuropathologists' Award for Meritorious Service. Further, Drs. Lysia Forno (1991; trainee in 1951), Lowell Lapham (1994; trainee in 1954), Henry deF. Webster (2001; trainee in 1956), and Margaret Norman (2008; trainee in 1968) were also recipients of this award. Other graduates who have served as President of the American Association of Neuropathologists include Drs. Webster, Donald Price, John Trojanowski, and Jeffrey Golden. Dr. Webster also served as President of the International Society of Neuropathology.

## Conclusion

The lineage of MGH Neuropathology can be traced from the great British and European neuropathologists of the late nineteenth and early twentieth centuries and from the earliest

neurologists at Harvard, through Drs. Kubik, Richardson, and Hedley-Whyte, and to the neuropathologists of today. The future of MGH Neuropathology promises to be even brighter than its past. It is a vibrant department, busy with clinical cases and populated by young physicians and physician-scientists who have superb clinical and experimental training. With the armamentarium of neuropathology now greatly expanded beyond the light and electron microscopes, MGH Neuropathology is poised to continue its tradition of disease description and discovery.

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