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A History of Neurological Surgery at UCSF 1912-2015



Written by Brian Dolan, Ilona Garner and Dorothy Porter

Dear Colleagues:

Since 1997, I have had the distinct privilege of leading one of the oldest and most established neurosurgery programs in the nation. The tradition of excellence in neurosurgical clinical care, research, and education at the University of California, San Francisco (UCSF) goes back over 100 years and has produced some of the most important advances in our field. This volume details and illustrates some of our many milestones and accomplishments.

Today our team at UCSF has the opportunity to review over a century of achievements that have brought us to where we are today, providing the best in patient care and the most cutting-edge research and education programs. Continually honored as the top neurosurgery and neurology program on the West Coast by *US News & World Report*, we have also earned the distinctions of highest academic productivity; highest level of NIH research funding; and most sought-after neurosurgical residency program.

As we reflect on the content found in this book, we are also excited to look toward the next 100 years. While the many experts that comprise our group today are taking on some of the toughest challenges in our field, our focus remains first on continuing to provide superb patient care in a changing health care landscape. Our services have expanded into major hospitals and clinics all over the Bay Area, and we are glad to partner with referring physicians here and across the nation for consultation and referrals.

The remarkable growth of neurosurgery at UCSF and throughout the rest of the nation since the early 1900s is quite simply astonishing. I hope you will find the stories in this book as interesting and inspirational as I have.

Sincerely,

A handwritten signature in black ink, appearing to read 'Mitchel S. Berger', written in a cursive style.

Mitchel S. Berger, M.D.
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Department of Neurological Surgery
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Rosegay H. A History of Neurological Surgery at the University of California, San Francisco. *Neurosurgery* 38: 4 (1996),794-805.

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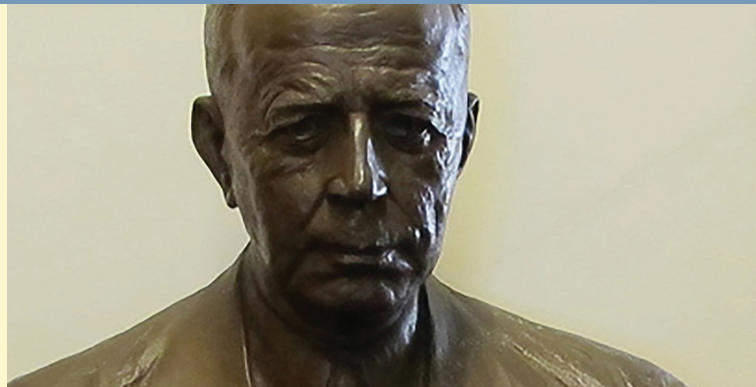
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Chapter One

The Origins of Neurological Surgery at the University of California



“The first neurosurgical case of any magnitude in the old UC Hospital was in 1912 in the fall or summer,” wrote Dr. Howard Christian Naffziger, recollecting his early years of practice in a draft autobiography that exists in the archives of the University of California, San Francisco. “The patient, a Mexican, was transferred from the S.F. Hospital service at the Laguna Honda site. It was a cerebellar decompression. Gradually other cases appeared. The neurosurgical work at the S.F. Hospital was mostly in traumatic surgery and at the UC Hospital it was elective in nature. The consulting work on neurology on the medical service came to the neurological surgeon.”¹

Howard Naffziger, MD, Chair of the Department of Surgery, 1929-1947, and first Chair of the Department of Neurological Surgery, 1947-1951.



Howard Naffziger was born in Nevada City, California in 1884. He attended Berkeley High School, the University of California, Berkeley, and the Medical School, graduating in 1908. During his surgical training at UC, Naffziger was greatly impressed with the surgical skills of Camillus Bush, a fellow Californian with a strong interest in surgery of the nervous system. Bush, a graduate of Johns Hopkins Medical School, ignited young Naffziger's interest in the new specialty and encouraged his further study at Johns Hopkins.

Naffziger was no mere chronicler of the early history of neurological surgery at the University of California. A surgeon whose achievements need little introduction to members of the present department, and indeed to the discipline of neurosurgery, Naffziger was recollecting a history to which he contributed so much.

Having passed away in 1961 at the age of 77, Naffziger is memorialized on campus through the Naffziger Surgical Society, the Naffziger Laboratories, portraits and bronze busts. Tributes to his medical skills endure through diagnostic and surgical eponyms: Naffziger's test, or bilateral jugular compression to localize the area of spinal nerve involvement that elicits the characteristic pain in cases of herniated intervertebral disk; Naffziger's syndrome, or scalenus anticus syndrome; Naffziger's operation, or the surgical relief of malignant exophthalmos. His contributions on the pineal shift in brain tumors, the replacement of bone in skull defects and his tentorium-splitting procedure for tumors of the brain stem and posterior fossa are celebrated in the annals of history.²

While the past century has seen neurological surgery build on such accomplishments to progress in many clinical and research



areas, what is striking about Naffziger's early work, and the origins of neurological surgery at UCSF, was that it was achieved under such trying technical and institutional conditions.

The Context of Early Neurological Surgery

In the first decades of the twentieth century, neurological surgery was truly in its infancy. No surgical suction cannula; no Bovie units (until 1926); no chemicals to reduce intracranial pressure, except for hypertonic salt solution; transfusions were rare. All trigeminal root sections were performed with the patient lying down in the recumbent position in a dental chair fashioned with a head and

In 1918, Naffziger went to France with his mentor, Harvey Cushing, as a member of the Allied Expeditionary Force. Cushing's surgical advances were brought to the field hospital by his young disciple. Naffziger summarized the success of battlefield neurosurgery in a manual published by the US Surgeon General at the end of the war.



neck support. In the late 1920s, an osteoplastic flap would take 6-7 hours. Brain edema was a problem during and after surgery, and brain fungus was not uncommon. All osteoplastic flaps were made by hand, using a hand-drawn perforator and burr, plus the Gigli saw.

For Naffziger – the son of immigrant Bavarian parents who became Midwestern farmers before starting a meat market in the mining town of Nevada City, California, in the 1870s – the world of medicine and surgery was completely foreign. His interest in medicine and science, he would later say, stemmed from his admiration of a country doctor who treated Naffziger’s broken leg when he was nine years old. Perhaps apocryphally, he claimed to have read a book about a brain surgeon while convalescing, thereby inspiring him to that calling. Certainly, however, he studied science at UC Berkeley between 1902 and 1905, at which point he entered the Medical Department of the University of California, part of the “Affiliated Colleges” of the University (at that time UC having only the Berkeley campus), in new

buildings at Parnassus Heights. As a young medical student, Naffziger was treated to a growing medical school that boasted a 1220-seat auditorium, “the finest dissecting room in the world,” and “spacious laboratories for pathology, bacteriology, chemistry, and physiology,” according to a contemporary UC brochure.³

Naffziger would be inspired by the cutting-edge, scientifically based instruction that aimed to make UC a leading training ground for medicine, until the great earthquake in Naffziger’s second year of medical school threatened that future. “In April, two days before the earthquake, [I] moved to the Nu Sigma Nu house on Willard Street, about 1412 or next door, and was there for the earthquake,” recalled Naffziger. “I was awakened by it with things falling around. We knew it was a catastrophe. ... Walked downtown [and was] in the Palace [Hotel] when the firemen drove everyone out. Got some rolls in a restaurant – looked around at the devastation and returned to Golden Gate Park where operating tables were set up opposite the



end of Haight Street. Did odd jobs, catheterizing patients, making visits, etc.”⁴ This was Naffziger’s most significant introduction to trauma surgery, and reaffirmed his early commitment to dedicating himself to surgical practice.

But in the years following the earthquake, the “Medical Department” of the University of California would witness further challenges to its infrastructure, curricular developments, and clinical services. (It would not become its

own campus until decades later, which impacted the Department of Neurological Surgery in ways that will be discussed further below.) With space physically destroyed, science departments and laboratories were relocated to the Berkeley campus, removing research sites from the proximity of hospital space, imposing a division of commitments among faculty and students. The distance to the San Francisco City and County Hospital at its location on



The disaster took a huge toll on the city's medical facilities—many of the city's hospitals were damaged or destroyed, including UC Medical Department's dispensary clinic at Montgomery Street and the Park Central Emergency Hospital near Golden Gate Park. The injured were evacuated to the Presidio's Post and General Hospitals in the far western portion of the city. The antiquated City and County Hospital, which had survived relatively undamaged, was quickly overloaded with patients.



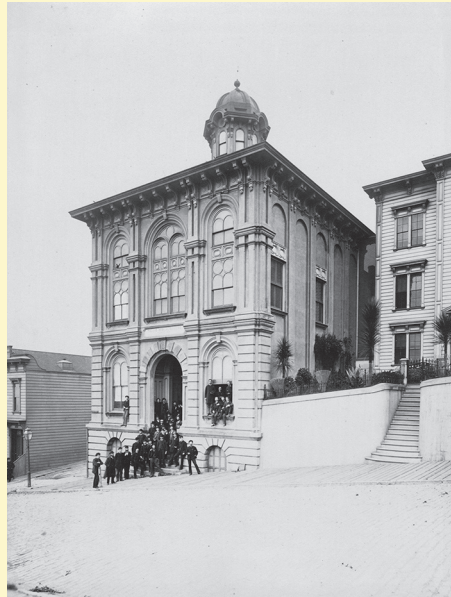
Potrero Avenue (where it started development in the 1870s), four miles across town from the education buildings, had led to other complaints, but in 1908 an outbreak of plague caused its closure and patients were transferred to barns and stalls at Ingleside Race Track off Ocean Avenue, near Lake Merced. Conditions were indicative of the limitations of clinical practice. “Our patients were in large wards or box stalls,” remembered Naffziger, “the latter were assigned to us according to the name of race horses remaining over the box stalls.”

How could a medical student, enduring such trials of clinical training, within a few years of graduating go on to spearhead major innovations in the development of neurological surgery at UCSF? While ultimately it

speaks volumes to the charisma of a dedicated practitioner, in fact these experiences and observations had a much wider impact. They fundamentally informed Naffziger’s dedication to creating a unique training program for neurosurgical residents.

He was an outspoken advocate for educational and clinical reform, possessing an awareness of what needed to be done to bring medical training to a leading position on the west coast. The development of neurological surgery at UC was intimately tied to the broader effort with which Naffziger was so involved to create and establish an institutional structure to support the practice of the specialty through departmental organization, hospital planning, and grant recruitment for laboratory research.

On the left, "Tent City," a camp set up in Golden Gate Park following the 1906 earthquake, with the UC Affiliated Colleges in the background. Below, the dissecting room at Toland Medical College. Right, Toland Medical College.



Within a week, over 100 refugee camps were set up throughout the city and more than 40,000 people took shelter in Golden Gate Park, where improvised outdoor hospitals served the sick and wounded, and outdoor kitchens were set up to feed the public. The Affiliated Colleges, located in what was once the far western section of the city at the end of the Masonic streetcar line, were now much closer to the center of the San Francisco population.

Naffziger was not just the first titled Professor of Neurological Surgery and pioneer of its departmental origins at UC, he was also Chair of the Department of Surgery (1929-1947), Chair of the Division of Neurological Surgery (1947-1952), Member of the Board of Regents of the University of California (1952-1961), officer in the Medical Corps of the US Army in WWI, Chief of the Surgical Service of the Letterman Hospital, and the president of seven medical societies, including the American Surgical Association, American College of Surgeons, and the Society of Neurological Surgeons. Remembered fondly by his contemporaries as compassionate, punctual, and deliberate, he was also often characterized as a perfectionist, irascible, and "almost merciless."⁵ Yet these were traits

necessary to move the bureaucracy along throughout the years and survive the storied career he had. Perhaps owing to his family's frontiersmen ambitions, his own rugged experiences working in quartz mines, or his eye-opening exposure to natural devastation, Naffziger had a strong personality.

Yet for all his accomplishments that informed the history of the Department of Neurological Surgery, leaving a legacy that would reappear throughout the hundred-year history outlined in the pages to follow, he was at heart a surgeon, focused on exacting skills and successful outcomes. Therefore consideration of Naffziger's clinical work, the foundation to his career, is useful to examine the state of the art in the early days of neurological surgery.

The Affiliated Colleges of the University of California, in San Francisco. In 1872, four years after the University of California was established and as the structure of the divisions of the University was still under development and buildings were still under construction in Berkeley, a “medical department” was established under the control of physicians in San Francisco.



The Education of a Surgeon

During Naffziger’s years as a medical student he became acquainted with Camillus Bush, an assistant in surgery and graduate of the Johns Hopkins School of Medicine, where he had studied under William Stewart Halsted. (Bush not long after died at the age of 32 from typhoid fever.) Impressed with Bush’s surgical techniques, Naffziger was urged to join the training program at Johns Hopkins led by Halsted and Harvey Cushing, highly regarded as the father of American neurosurgery. Naffziger moved to Baltimore in 1911, and, in the words of Allen Johnson, a professor of surgery at UCSF, “his experience helped

crystallize not only a devotion to surgery of the nervous system but also a dedication to improving the standards and techniques of surgical instruction.”⁶

An example of a case illustrates the skills Naffziger was acquiring. Owing to historical research conducted in the archives at Johns Hopkins, in a project overseen by Mitchel Berger and Alfredo Quiñones-Hinojosa, we have a good account of the types of surgery to which Naffziger was exposed while studying under Cushing. Clinical records reflect 27 clinical cases documenting Naffziger’s direct involvement with patients of whom 26 underwent operative interventions in 38 procedures.⁷ Naffziger was involved with writing admissions notes including medical history



*Left, City and County
Hospital, San Francisco,
1919.*

and physical exam, progress notes, and discharges. He was involved with one peripheral nerve case, 24 intracranial cases, and two spine cases. On December 26, 1911, a 13-year-old girl presented with a tumor of the left temporal lobe. Naffziger's admission note reads: "Girl about 12 years of age, pale and frail looking. Intelligent and quick to answer. ... [Neurological symptoms:] Cerebellar. Dizziness (see above). No ataxia of arms or legs. No nystagmus. Adiaochokinesia – neg. No Romberg."

Naffziger's notes on this case continued for ten pages, a sign of his reputed meticulousness. Cushing reviewed the information, adding his own marginal notations: "Suboccipital headaches. Hydrocephalus? Tense decompression and spurt of

lumbar puncture fluid." Cushing concluded: "The extraordinary bizarre features of this patient have puzzled us greatly ... there are certain things that made it seem possible that after all the lesion might be in the right temporal lobe. In the first place the possibility of a sensory aphasia, secondly the smacking of the lips that Dr. Naffziger has noted."⁸

The surgical case notes reflect Cushing's predilection for integrating technology in clinical practice and his meticulous operative techniques. These are features that Cushing had just advocated in addresses given the previous year to two medical groups in Ohio. In a publication summarizing these talks, Cushing said that his remarks on neurological surgery provided a chance to "contrast with [the field's] former

barrenness the relative fertility now shown in this small acreage." He described recent advances in the diagnosis, surgical treatment, and post-operative complications of brain tumors while noting that less progress had been made since 1905 in the treatment of tumors in the spinal cord. He noted that surgery to treat infantile hydrocephalus and epilepsy, while

"The clinical applications come primarily and exclusively as the result of serious experimental research"

providing some relief, did not address the underlying causes of these conditions. He emphasized the importance of basing surgical advances on laboratory research – "the clinical applications come primarily and exclusively as the result of serious experimental research" – and advocated the development of neurosurgery as a distinct specialty. Cushing emphasized the ongoing need for greater understanding of how to alleviate pressures within the brain and the circulation of cerebrospinal fluid as they related to the presence and impact of tumors. He also proved prescient when he commented that, "it requires no wild imaginings to foresee the day of transplanted organs and members."⁹ None of these points would have been lost on Naffziger, and indeed they suggest the foundation of his own philosophy of neurosurgical progress that materialized in the disciplinary developments

upon his return to the West Coast.

Naffziger returned to San Francisco in 1912 and entered private general surgery practice, but was motivated to join the UC faculty and forge a new path in the Affiliated Colleges. Indeed, in Naffziger's own words, "I was so impressed [with the training at Johns Hopkins] that I went to [Dr. Arnold] D'Ancona, then Dean of

Medicine [at UC] and Hospital Superintendent, and convinced him we ought to start a resident system at UC. He asked what I would recommend. I had the temerity to suggest that he keep me on a second year as resident – pay me board and room and \$75 per month. I would supervise interns on all services, make notes on cases, do the abnormal obstetrics, assist in the operating room and try to make rounds."¹⁰

Naffziger's temerity led to triumph. His experiences and early articulations of the value of residency programs would define an important part of his life-long campaign to reform medical education and create training oversight for neurological surgery. In 1913, Naffziger was appointed an Assistant in Surgery, in the Department of Surgery, with an annual salary of \$900.¹¹

As recounted by Harold Rosegay in his history of neurosurgery



Howard Naffziger, MD

at UCSF, and who reviewed Naffziger's early patient charts, by 1920 Naffziger had performed 21 decompressions for brain tumor, seven tumor verifications, and two tumor removals. He performed 15 osteoplastic craniotomy for epilepsy related to trauma or congenital brain lesions, 15 cases of craniotomy or subtemporal decompression for trauma, 14 cases of neurorrhaphy and neurolysis, six hydrocephalus procedures, mainly the Balkenstich operation, six laminectomies for spinal cord tumors

and two for acute trauma, six cases of root section, neurectomy, or alcohol injection for trigeminal neuralgia, and eight cases involving either drainage of brain abscesses, cranioplasty, or cranial decompression.¹² These numbers matched Cushing's surgical record for the same decade. Naffziger was building his reputation and establishing his expertise rapidly.

Within this timeframe there was also a two-year gap in clinical service at UC when Naffziger served with the US Army, being

commissioned as a Captain in 1917. He then became Head of Neurosurgery in the Medical Unit at Camp May, New Jersey, with the rank of Lt. Colonel. He served in France with the American Expeditionary Forces and was assigned to Base Hospital 115. He was then reunited with his mentor Dr. Harvey Cushing with whom he served on front-line neurosurgical teams. Drawing from his experiences, he helped prepare a neurosurgical manual published by the Surgeon General's Office. He concluded his military tenure at the Letterman Army Hospital in San Francisco where he was Chief of Surgical Services.¹³

By the time Naffziger returned from military service and resumed his role on the faculty at UC in 1919, he had much to reflect on regarding the development of neurological surgical practice and the possibilities it afforded patients through dedicated service. Much had happened in the past ten years, both for Naffziger and the discipline more generally, to give Naffziger reason to think that the time was right for neurosurgery to claim its place within UCSF and the wider profession. In his own words:

“During these years [1912-1917], up to the interruption by World War I, there was a growing appreciation by the profession at

large that there was a specialty of neurological surgery. Many talks at medical societies were given. The head operating room nurses from numerous hospitals on both sides of the bay were organized and desired to become familiar with neurosurgical techniques, preparation of the patient and the field of operation, special instruments and suture material and dressings. During the two year interruption by the War, but few cases were operated upon. Returning in the fall of 1919, I decided to give up general surgery entirely. Widening appreciation of neurological surgery made heavy demands.”¹⁴

For multiple reasons – personal and professional – now was the time to focus on pursuing neurological surgery.

Endnotes

- 1 Naffziger, Autobiographical Notes, p. 16, MSS 97-004 Box 1, Folder 2.
- 2 Kennedy, in festschrift (1944); *Alumni Faculty Association Bulletin* (School of Medicine, UCSF) 29: 1 (1985).
- 3 For more historical background, see the account written by Dr Nancy Rockafellar and Dr Brian Dolan, http://history.library.ucsf.edu/1868_parnassus.html.
- 4 Naffziger, Autobiographical Notes, p. 24, MSS 97-004 Box 1, Folder 2.
- 5 Milton J. Chatton, "A Reminiscence," in *Alumni Faculty Association Bulletin* (School of Medicine, UCSF) 29: 1 (1985), p. 3.
- 6 Allen Johnson, MD, "History of the Department of Surgery at University of California, San Francisco," Surgery Grand Rounds, May 1995. Typescript in UCSF Archives, SOM, Department of Surgery, S 1:1. In his autobiographical notes, Naffziger says that he "enquired of him [Dr. Camillus Bush] about his surgical training and learned of the Hopkins resident system."
- 7 Courtney Pendleton, Mitchel Berger, Alfredo Quiñones-Hinojosa, "Go East, Young Man: Howard Christian Naffziger's Early Training at the Johns Hopkins Hospital and the Development of Neurosurgery at the University of California, San Francisco," unpublished typescript.
- 8 Pendleton, et al. (op cit.), p. 4.
- 9 Harvey Cushing, "The special field of neurological surgery: Five years later," *Bulletin of Johns Hopkins Hospital* 21 (1910), 325-339.
- 10 Naffziger Archive, UCSF Archives and Special Collections, MSS 97-004 Box 1, Folder 2.
- 11 SOM Faculty Minutes 1900 – [], AR 24.2.
- 12 Harold Rosegay, "A History of Neurological Surgery at the University of California, San Francisco," *Neurosurgery* 38: 4 (1996), 794-805, p. 794.
- 13 Chatton, "Howard Christian Naffziger," (op. cit.), pp. 9-10.
- 14 Naffziger Archive, UCSF Archives and Special Collections, MSS 97-004 Box 1, Folder 2, p. 16.



Chapter Two

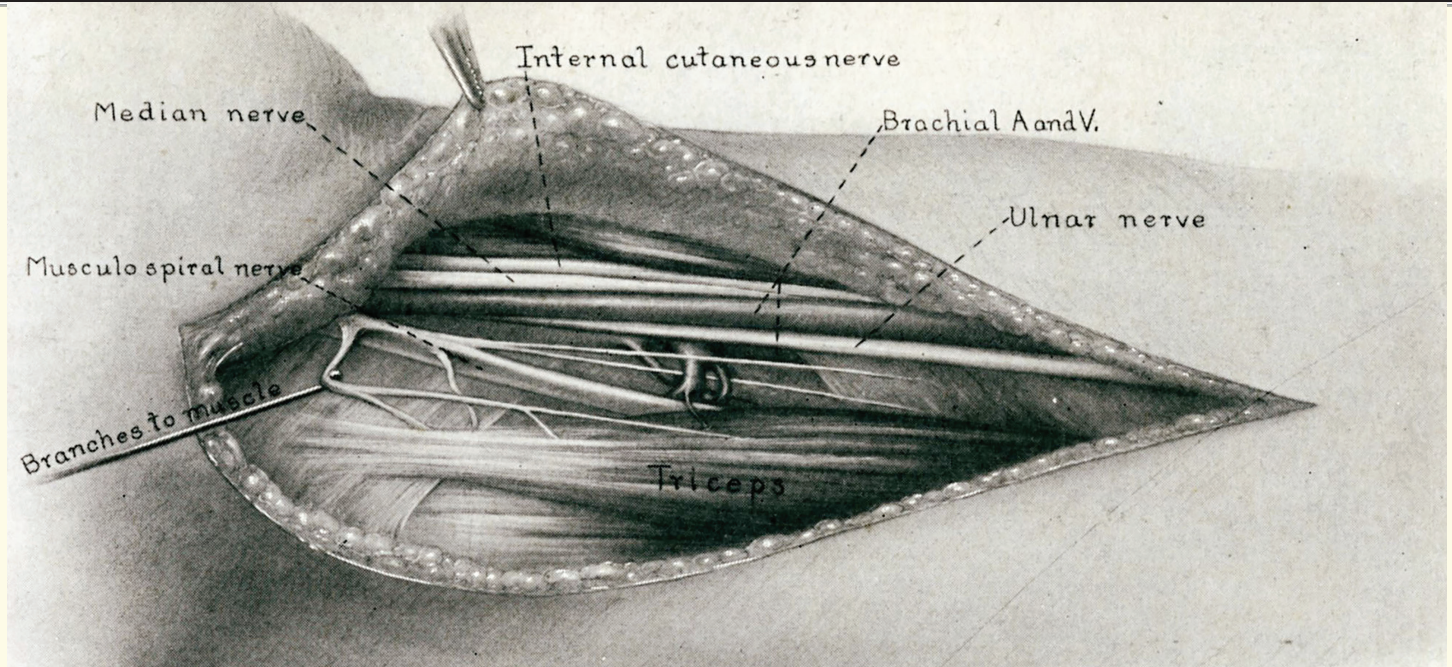
Developing Clinics in Neurological Surgery



“The ideal surgical hospital would be one whose senior appointees after a broad general surgical training would be encouraged by continuous services to concentrate their work on special subjects – as many subjects as there are men who may be qualified pathfinders. I realize, of course, that such positions cannot be created outright and men found to fit into them. Rather, it will happen that positions must be built around such individuals as are available and must grow in accordance with the individual’s capabilities. A junior staff in the meantime would carry on the general routine work, any subdivision of which ... may become special tomorrow through some unexpected discovery, and again at some later day lapse back once more into the general mill, but always, it is to be hoped, on a higher plane.”¹

- Harvey Cushing

Dr. Harvey Cushing working at his desk.



The decade of the 1920s saw professional expansion nationwide and institutional developments in neurological surgery at the University of California. In 1920 the Society of Neurological Surgeons was organized at the Peter Bent Brigham Hospital in Boston. By the end of the decade there were 29 members; by 1950 there were 61. Naffziger had reason to be encouraged about the future of the discipline, and this decade saw a concerted effort to strengthen the clinical and teaching services at UC.

The first step here was to ensure that junior faculty had the appropriate background training. Without a critical mass to launch its own program just yet, Naffziger did what Camillus Bush did for him and that was select the most promising surgical assistants and recommend they study with Cushing. One of the first under Naffziger's purview was Howard Fleming.

Fleming received a BS in 1914, and his MD in 1917, both from the University of California. His residency in surgery was served at San Francisco Hospital, his internship at the University of California Hospital. In 1919 he went to Peter Bent Brigham Hospital, where Cushing had been appointed surgeon-in-chief, and became assistant resident to Cushing. After a year in Boston, Fleming returned to his native California and was appointed assistant in surgery in 1921. Another addition to Naffziger's team was C.E. Locke, who had succeeded Fleming as Cushing's surgical assistant at Brigham and in 1922 was awarded a \$2,300 fellowship by the National Research Council in neurological surgery for one year, which was used to further his training at UC. It was a prestigious and useful award for the Department of Surgery, and it helped raise neurosurgery's profile as a "sub-department" – a term used

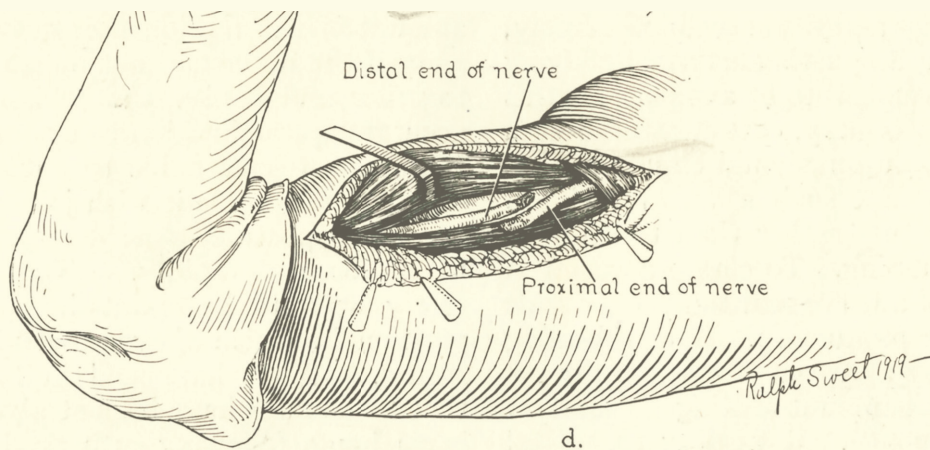


Fig. 6. Sciatic nerve. *a*, Sections of neuroma; *b*, sutures in place; *c*, Sutures tied; *d*, gap overcome by knee flexion.

by the Office of the President of the University, which would become synonymous with “division,” and even “department,” in the loose nomenclature of university infrastructure in these early decades. In an annual bulletin published by the Office of the President, it was noted that the “services of a full-time man resulting from this grant have permitted rapid progress in research and instruction in this sub-division. Several graduate house officers at the University Hospital together with fifth year men have aided in the study of the research problems. Attention has been chiefly directed to the anatomy of sub-arachnoid space, the circulation of the cerebro-spinal fluid, and to factors affecting nerve and muscle regeneration following peripheral nerve injuries.”²

Things got busy fast. It was reported that in 1922, the amount of clinical and operative work in neurosurgery had increased 25% over the previous year. It

was timely and useful to have Fleming and Locke on the roster, and in 1923 the two surgical assistants relieved Naffziger of sole responsibility of neurological surgery operations by beginning to operate with assistance from the surgical residents.

As professional relationships were forged and collaborations formed, important and innovative work was beginning to yield. In 1923, Naffziger and Locke performed a transtentorial approach beneath the occipital lobe, in which an exophytic glioma was partially removed from the cerebellopontine angle. “This was one of the cases,” noted Harold Rosegay, “that led to the important article concerning alternative ways of relieving impaction in the posterior fossa.”³

Brief consideration of Naffziger’s article, along with the elegant illustrations provided with them, captures the state of knowledge and innovation at the time.

Above left and right: illustration by Ralph Sweet featured in “Methods to secure end-to-end suture of peripheral nerves” by Howard C. Naffziger, MD, Surgery, Gynecology & Obstetrics, 1921.

“Since the days of Lister, the osteoplastic bone flap of Wagner with its wide exposure has replaced the measurements of cranial topography and the selection of a much debated localizing point for a trephine opening. Likewise craniectomies have given way to plastic operations upon the skull except in the subtemporal and suboccipital regions. In these areas where other structures than bone may give adequate protection to the brain, such openings have their especial decompressive advantages. The temporal and cervical muscles act as protective coverings and at the same time restrain excessive or harmful herniations. Brain herniation through properly placed decompressions will cause no disabling symptoms. Operative procedures tend to become standardized. While for decompressions and approaches to near-by structures these craniectomies have especial advantages, the plastic operations are generally used for the cranial vault. ...

Less systematic attention has been given to surgical approaches to those structures in front of the cerebellum and between it and the third ventricle. This portion of the brain stem, the pons, tentorium, and pineal region, has received little notice. The surgery of this area involves special considerations. The principle of decompression to permit expansion outside of the cranial cavity is old. Yet with a certain part of the cranial cavity impactions occur. ...

The subtentorial space may be enlarged by wide opening of the tentorium or by section of the tentorium including the incisura tentorii. The approach is best made from above, through what we have termed the occipital flap. The field of usefulness of this operation has widened in that it also serves as a supratentorial approach to certain infratentorial tumors. It permits access to the pons, to all tumors which spring from the tentorium and the posterior half of the falx, to the entire occipital lobe and all the midline structures. Ready exposure of the upper and anterior surfaces of the cerebellum is made, areas which cannot be uncovered by a suboccipital operation. Enlargement of the posterior fossa gives added opportunity for expansion upward. The brain stem is no longer crowded down into the foramen magnum. ...

*Excerpt from
Howard Naffziger,
“Brain Surgery with
Special Reference
to Exposure of the
Brain Stem and
Posterior Fossa;
The First Principle
of Intracranial
Decompression,
and the Relief of
Impactions in the
Posterior Fossa,”
Surgery, Gynecology,
Obstetrics 46
(1928), 241-248.*

CLINICAL SURGERY

FROM THE DIVISION OF NEUROLOGICAL SURGERY, UNIVERSITY OF CALIFORNIA

BRAIN SURGERY

WITH SPECIAL REFERENCE TO EXPOSURE OF THE BRAIN STEM AND POSTERIOR FOSSA; THE PRINCIPLE OF INTRACRANIAL DECOMPRESSION, AND THE RELIEF OF IMPACTIONS IN THE POSTERIOR FOSSA

BY HOWARD C. NAFFZIGER, M.D., F.A.C.S., SAN FRANCISCO
From the Division of Neurological Surgery, University of California Medical School

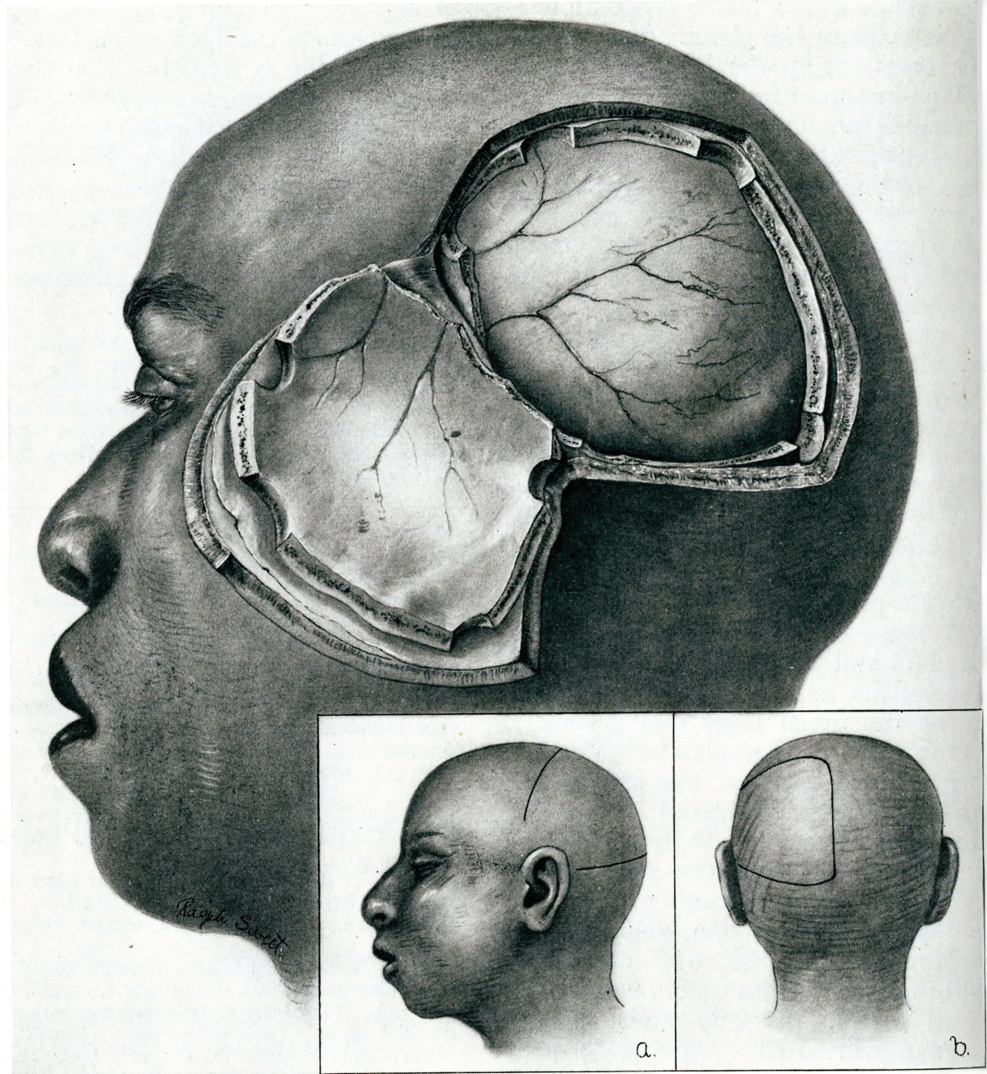
THE fascination of brain surgery lies in its difficulties. More than in the surgery of other parts, the mere opening and closure of a wound is a major procedure. It involves a difficult approach through exceptionally heavy and resistant structures to organs vital, delicate, and readily traumatized. It is laborious, time-consuming, detailed work with constant possibilities for hæmorrhage. The surgical treatment of the lesion itself often involves less time and effort than the exposure of it and the closure of the wound. The vascularity of the coverings and the special technical methods required to open the skull without injury to its contents both present their problems and their risks. For the future of the patient, proper closure is of the highest importance. On the surgeon it makes special demands. The slow, painstaking, detailed closure at the conclusion of a trying operation demands a self-exacting thoroughness not often called upon in other situations. More rapid but less detailed methods of repair bring in their train late hæmorrhage, herniations, brain damage, fungi, and hideous, harmful protrusions and scars. Training in this branch of surgery necessitates a degree of gentleness and attention to detail seldom acquired in the surgery of less delicate structures. Special methods are demanded for the control of bleeding and much experience in avoiding it. The elaboration of the technique of neurological surgery is evidence of the necessities though simplification of technique is always desirable.

Since the days of Lister, the osteoplastic bone flap of Wagner with its wide exposure has replaced the measurements of cranial topography and the selection of a much debated localizing point for a trephine opening. Likewise craniectomies have given way to plastic operations upon the skull except in the subtemporal and sub-

occipital regions. In these areas where other structures than bone may give adequate protection to the brain, such openings have their especial decompressive advantages. The temporal and cervical muscles act as protective coverings and at the same time restrain excessive or harmful herniations. Brain herniation through properly placed decompressions will cause no disabling symptoms. Operative procedures tend to become standardized. While for decompressions and approaches to near-by structures these craniectomies have especial advantages, the plastic operations are generally used for the cranial vault.

For operations upon the hemispheres—the parietal, frontoparietal, and frontal osteoplastic flaps are used. All have their bases in the temporal region. With the thin squamous portion of the temporal bone in this location they break back readily. The temporal muscle and fascia act as a hinge. With the flap reflected, removal of that portion of the bone beneath the temporal muscle permits leaving a decompressive opening after the flap has been replaced. These large flaps permit of wide exposure. Elevation of the frontal and temporal lobes gives access to the structures of the chiasmal region. The entire anterior fossa and the anterior portions of the middle fossa can be reached.

Less systematic attention has been given to surgical approaches to those structures in front of the cerebellum and between it and the third ventricle. This portion of the brain stem, the pons, tentorium, and pineal region, has received little notice. The surgery of this area involves special considerations. The principle of decompression to permit expansion outside of the cranial cavity is old. Yet within a certain part of the cranial cavity impactions occur.



*Fig. I. The combined soft tissue and bone flap are on their pedicle.
The vessels of the dura run from before backward.*

Naffziger's Figure 2: "With the dura exposed, ventricular puncture is performed and the ventricles well emptied. Nearly all of the lesions for which this operation is performed are associated with an internal hydrocephalus. The emptying of the ventricle permits of easy elevation of the occipital lobe and wide exposure."

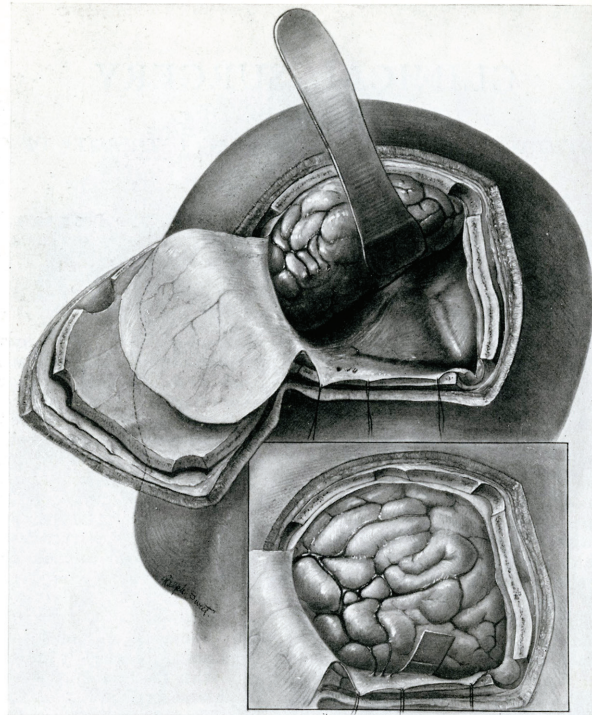


Fig. 2. The flap of dura is turned aside on its pedicle with blood supply unimpaired. The posterior lobe is retracted forward away from the tentorium.

"Incision is made in the tentorium. Occasionally irregular venus sinuses may be seen in the tentorium but can be controlled. The incision in the tentorium is widened in all directions up to the petrous bone anteriorly, to the sinus rectus mesially, and to the lateral sinus. An occasional vein bridges between tentorium and cerebellum and requires clipping. With this opening the upper surface of the cerebellar lobe is exposed over a wide area. (Fig. 3)

Retraction of it backward and laterally gives an exposure of the angle and the pons. The seventh and eight nerves are seen below and the fifth root toward the midline."

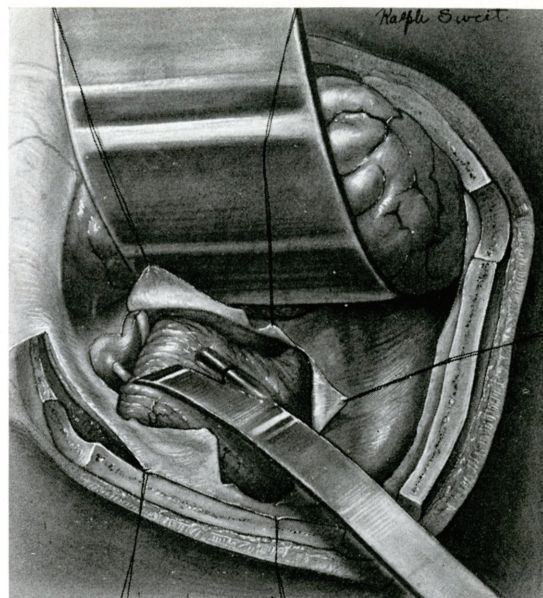


Fig. 3. The cerebellum and nerves from the base of the brain are exposed after incision of the tentorium.

Naffziger's Fig. 4:
 "In individuals who have previously been subjected to a suboccipital operation, the occipital flap may be modified. If there has been a suboccipital crossbow incision, one lateral half of the incision may be used to form the posterior margin of the occipital flap."

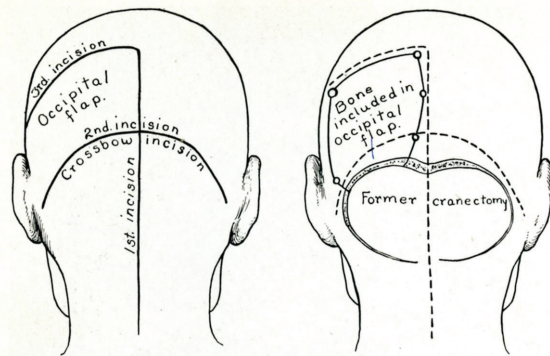


Fig. 4. Lines of incision.

The General Technique of Osteoplastic Flaps

• • • *Selection of the site of incision taking into account the area to be explored and leaving an adequate pedicle for the flap circulation and marking of the site should precede a firm draping of the field. Cross hatching of the line of proposed incision will facilitate proper matching of the margins upon closure. Digital pressure of assistants on each side of the incision is used to control bleeding and retract the margins of the wound. ...*

For primary bone openings a broad perforator, the point of which will pass through to the dura while the broad portion is still engaged, is safe. If the operator is careful to test bone thickness by percussion he will avoid possible accidents when dealing with the paper thin areas occasionally met. In placing the perforator openings it will be found that it is desirable to have the base of the bone flap near its hinge narrower than the free margin. If the two perforator openings nearer the base are placed to keep this in mind the flap when replaced will lie in position more satisfactorily. Five perforator openings in all are usually sufficient. ...

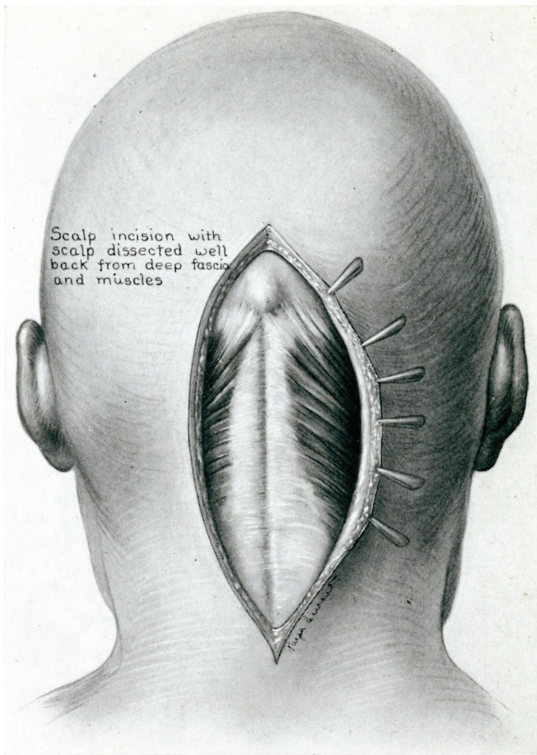


Fig. 5.

Naffziger's Fig. 5: "Certain technical points should be observed to obtain the best exposure. The midline incision should extend from about 4 centimeters above the external occipital protuberance downward to the fifth cervical spine or lower and is carried through the scalp down to the deep fascia."

Naffziger's Fig. 6: "After a similar separation on the opposite side, the area of exposure is increased by cutting the deep fascia and muscular attachments to the right and left of the torcula for a distance of about 3 to 4 centimeters. A fringe of deep fascia and muscle is left for subsequent suture."

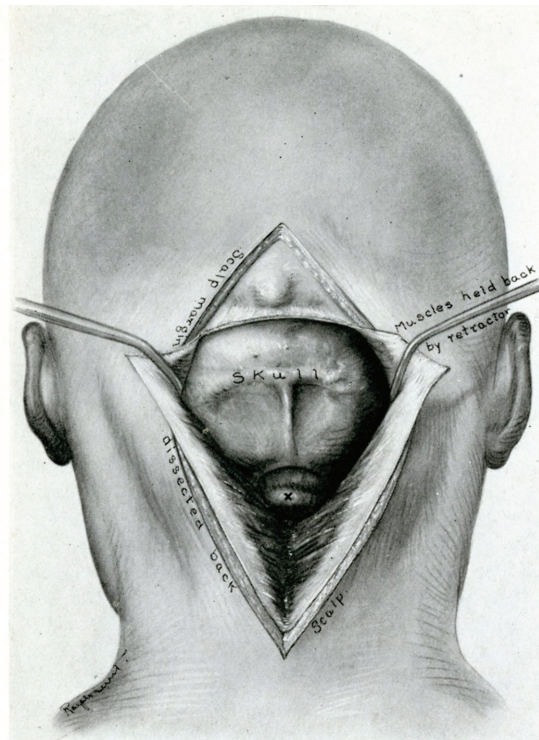
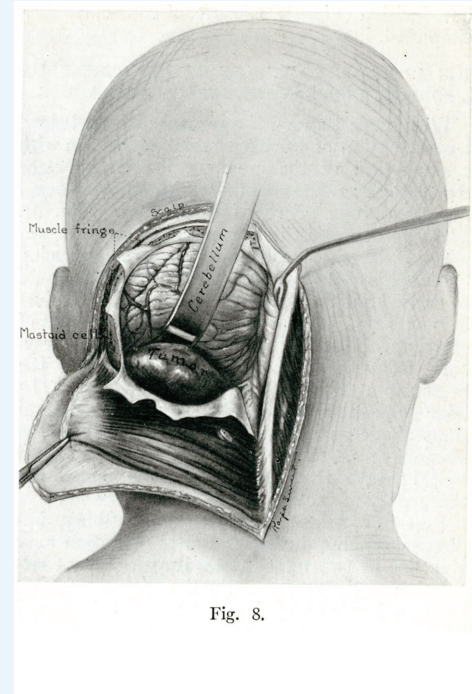
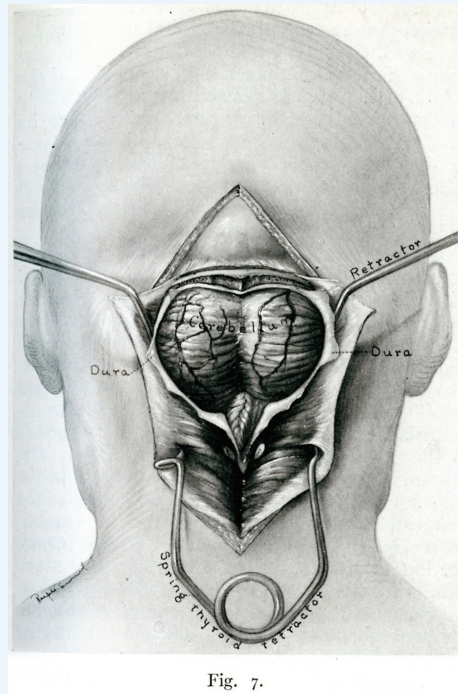


Fig. 6.

Naffziger's Fig. 7: "The nicking of the firm ligamentous attachments to the foramen magnum and the atlas, and the use of spring thyroid retractors give a wide exposure and permit the same bone removal, dural opening and opportunity for decompression, and the necessary intracranial work as the wider crossbow incision."

Naffziger's Fig. 8: "With angle tumors, if approached from below, a combination of the above midline incision with a single half of the crossbow incision shortens the procedure considerably without sacrificing the advantages of the full crossbow."



The Approach to Tumors of the Cerebellopontile Angle by the Suboccipital Route

• • • *As in the surgery of other regions, a satisfactory exposure of the lesion is essential. For many of the lesions in the posterior fossa the crossbow incision of Cushing or some of the simplifications of it are satisfactory. For the approach to lesions high in the angle, it leaves much to be desired. The methods here presented have been found helpful.*

By means of the occipital flap a transtentorial approach can be made. It affords access to the upper and anterior surfaces of the cerebellum, to the fifth nerve, and other nerves of the angle. This is an ideal approach to lesions of the tentorium, the posterior half of the falx cerebri, the occipital lobe, the pons, and pineal region. Section of the tentorium and incisura tentorii affords a method of intracranial decompression. By means of it, hydrocephalus from impaction in the posterior fossa have been relieved when other measures have failed.⁴ ...

“The fascination of brain surgery lies in its difficulties.”

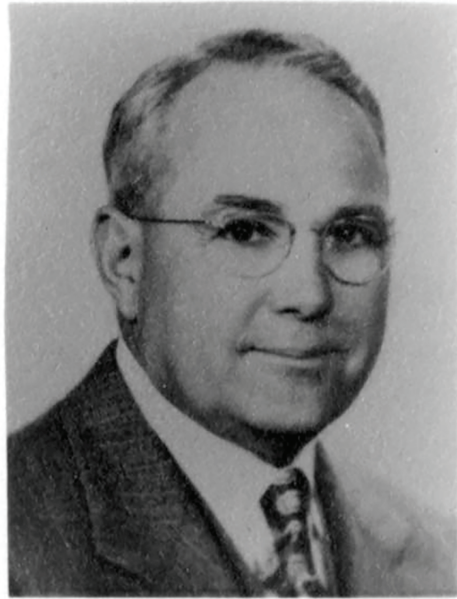
— Howard Naffziger

Around the time that Naffziger was working on the operative techniques just reviewed from this 1928 article, understanding the localization of posterior fossa tumors was becoming more advanced based on diagnostic innovations. For example, in 1918, Walter Dandy’s development of ventriculography supplemented the physical exam to localize tumors, further enabling the certainty of surgical intervention. Thus Naffziger’s technique helped refine a procedure that would become more common.⁵ Yet as innovative as this was, it was only the beginning of a challenging path to providing safe operative procedures on the cerebellum and reducing mortality rates.

The next year Naffziger and Locke composed an article on cerebral subarachnoid pathways, while the neurosurgical community – Walter Dandy, Wilder Penfield, Charles Frazier, and others – were continuing to offer views about what kinds of

incisions (midline vs cross bow vs straight linear incision) worked most effectively. But this is what made neurological surgery worth the dedication and concentration. As Naffziger famously declared, “The fascination of brain surgery lies in its difficulties.”⁶

Neurological surgery was also becoming a discipline that was growing nationwide, and talent trained under the likes of Cushing or Naffziger were bound to be difficult to keep. In 1924, C.F. Locke was recruited to the Cleveland Clinic as the first neurological surgeon on the staff. Sadly, in 1929, a devastating fire erupted in the hospital there, burning tens of thousands of nitrocellulose X-ray films that were stored on wooden shelves, releasing toxic fumes. Locke was on duty, forced to escape through a skylight. But within hours he, along with other survivors, became cyanotic and had shortness of breath, developing pulmonary edema. He died hours later.⁷



Ottiwell W. Jones, Jr.

Ottiwell Wood Jones, Jr., was born in San Francisco in 1897. He received his undergraduate degree in 1920 and his medical degree 1925, both from the University of California, where he also interned (1924-25) and did his residency (1925-28) under Howard Naffziger. After 49 years in practice, Jones became Professor Emeritus in 1968. Throughout his academic career, he was affiliated with the Postgraduate Training Program at Franklin Hospital-University of California and trained over 40 neurosurgeons under his tutelage. Jones passed away in 1987.

After Locke's move to Cleveland, Naffziger selected Ottiwell Jones, Jr., to be his full-time resident, a position he held from 1925 to 1928. Jones was a San Francisco native and graduate of UC for undergraduate and medical school. With a passion for science and a vibrant mind, he went to the Royal Victoria Hospital in Montreal with a fellowship in Neuropathology at McGill, where he studied under the supervision of Wilder Penfield and William Cone. While there he concentrated his attention to the study of brain tumor pathology and the development of astroglia and microglia, writing a paper on the latter cell type. After Jones finished his fellowship, he returned to San Francisco and joined the faculty at UC, where over the ensuing half century he would forge a productive and fruitful career.

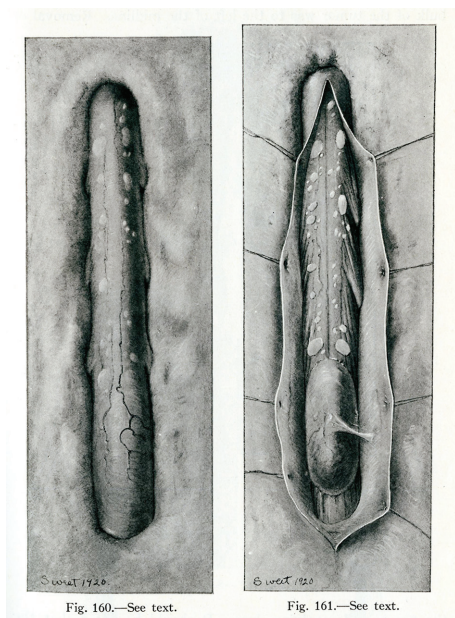
A successor to Ottiwell Jones, Howard Jones was brought on as neurosurgical resident from 1928 to 1930. Born in Stockton, California, Howard Jones also received his undergraduate and medical degrees from the University of California and went on to develop a special interest in spinal injuries and peripheral nerve damage.

The early years of the 1920s saw the publication of a number of important articles where Naffziger not only demonstrates his clinical skills by presenting cases where acute reasoning and judgment aided successful surgical outcomes, but lays the foundation for his later advocacy of enhanced diagnostic ability based on thorough neuropathological knowledge. A look at his articles illustrates this. What is striking about these articles is the attention and encouragement

given to the development of clinical skills that, on the one hand, assists in diagnosis without the aid of technologies that might even be superfluous for these cases today, showing the timelessness of the art of diagnosis in medicine, and on the other hand, show the depth of commitment to pre-surgical skills that Naffziger championed.

Naffziger's 1922 article on spinal cord tumors, for instance, laments that surgical attention often comes late in the onset of paralysis, even though better awareness of neuropathological symptoms could lead to earlier diagnosis. He presented

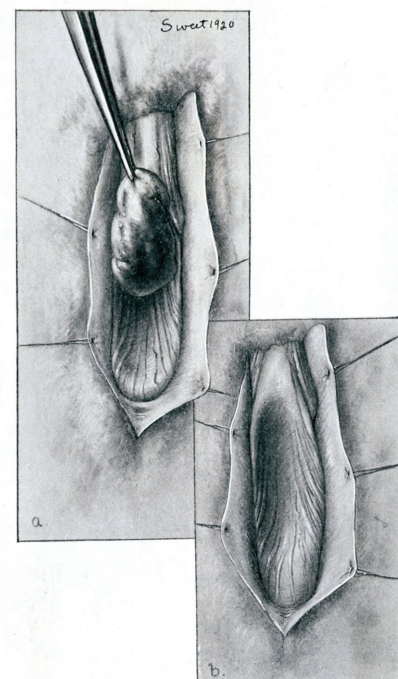
six cases for his clinic where patients had tumors of a pathologic group that was particularly amenable to surgical treatment, but diagnosis was missed by a succession of earlier investigations. "For each of the cases here presented there have been from four to twenty medical attendants before the diagnosis was made and treatment given," wrote Naffziger. "It would seem that the feeling that spinal cord tumors are very infrequent is largely responsible for this and also that syphilis is given undue prominence. The diagnosis of spinal



Figures 160 & 161, referring to a 31-year-old woman with pain in back and hips that was found to be caused by spinal cord tumor. "The dura showed definite pulsation at both upper and lower limits of the exposure. The dura in the region of the eleventh and twelfth lamina showed several vessels of considerable size." Shining through the dura were approximately 25 white plaques.

Images featured in "Spinal Cord Tumors (Arachnoid Fibroblastomata)" by Howard C. Naffziger, MD, *The Surgical Clinics of North America*, 1922.

Fig. 162: "Upon opening the dura the tumor was found on the dorsal surface of the cord at about the junction of the eleventh and twelfth dorsal vertebra."



Naffziger's figures from his pioneering article on spinal cord tumors, showing part of a series of diagrams charting a progression of hyperesthesia in a patient with symptoms that developed over a ten-year period.

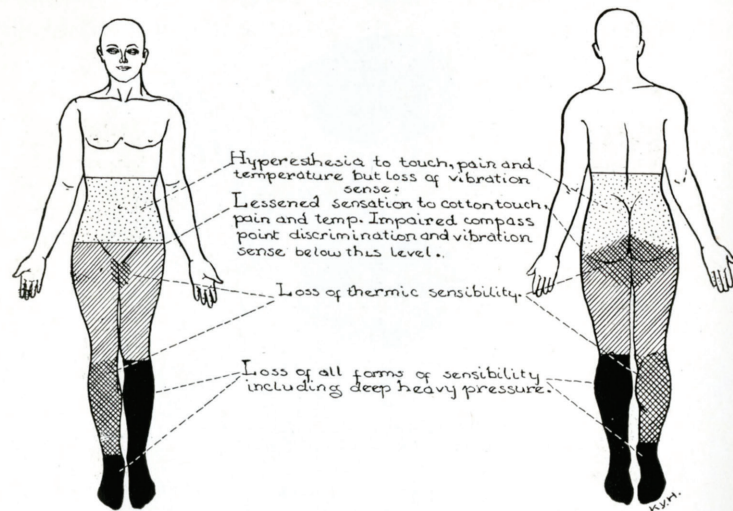


Fig. 165.

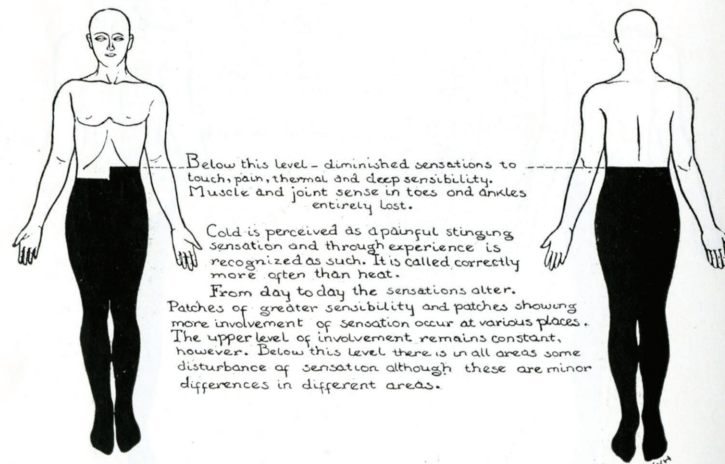


Fig. 166.

cord compression is not difficult. A slowly oncoming paraplegia or quadriplegia with a constant upper level of sensory involvement usually tells the story regardless of the details of the involvement."⁸

Taking the reader through the clinical notes case by case, we see the thoroughness of the physical exam and discussion of the complications of interpreting the patients' reports of pain amid varied sensory phenomena in the early days of dermatome mapping.

Naffziger's 1923 article on head injuries further explores themes of the importance of skilled clinical judgment in physical exam and assessment, raising challenging questions about the conditions that should be met to determine the indication of surgery. A series of examples of head injuries encourages his readers to develop diagnostic skills that render hidden trauma visible.

CLINIC OF DR. HOWARD C. NAFFZIGER
 UNIVERSITY OF CALIFORNIA HOSPITAL
 (FROM THE DIVISION OF NEUROLOGICAL SURGERY)

HEAD INJURIES. INDICATIONS FOR SURGICAL TREATMENT

IN the main there is a fairly general agreement that depressed fractures should have the depression relieved; that perforating and penetrating wounds should be surgically cleaned at the earliest opportunity. There is not the same divergence of opinion regarding the surgical handling of these cases nor the difficulty in decisions that there is in another larger group.

It is the case that is brought in without a skull depression or a penetrating wound and is in a serious condition from a head injury that taxes our judgment and makes decision difficult. In such cases there is usually a fissured fracture or fractures of the vault or base. The evidence of the former is found in the hemorrhage beneath the scalp along the area of bleeding, recognizable by the pitting on pressure over this area. The associated tenderness along the line of fracture assists us in the conscious patient. Roentgenograms of each side of the skull and the front and back add to our clinical information. Diploic and arterial vessel markings of the skull can ordinarily be differentiated from the fracture lines.

With the fractures of the base, the bleeding from the ears, the later ecchymoses over mastoid, and the horseshoe ecchymoses from it around the auditory meatus attract attention to the fissures of the petrous bone. The bleeding from the nose or vomiting of swallowed blood, the ecchymoses, subpalpebral and subconjunctival, in the absence of direct injury to the soft tissues, are important findings, and assist us in forming a judgment.

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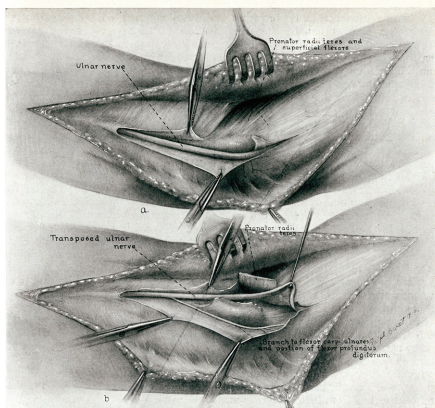


Fig. 1. Ulnar nerve. a, Normal route; b, transposed route.

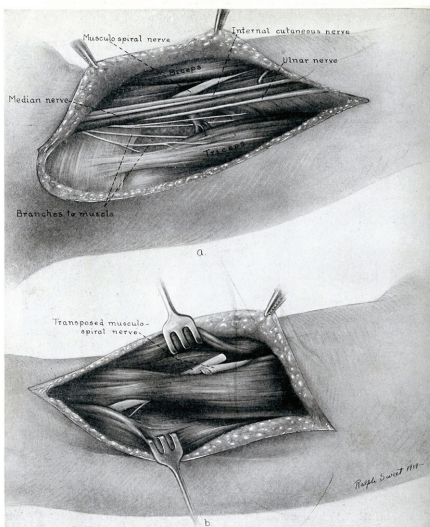
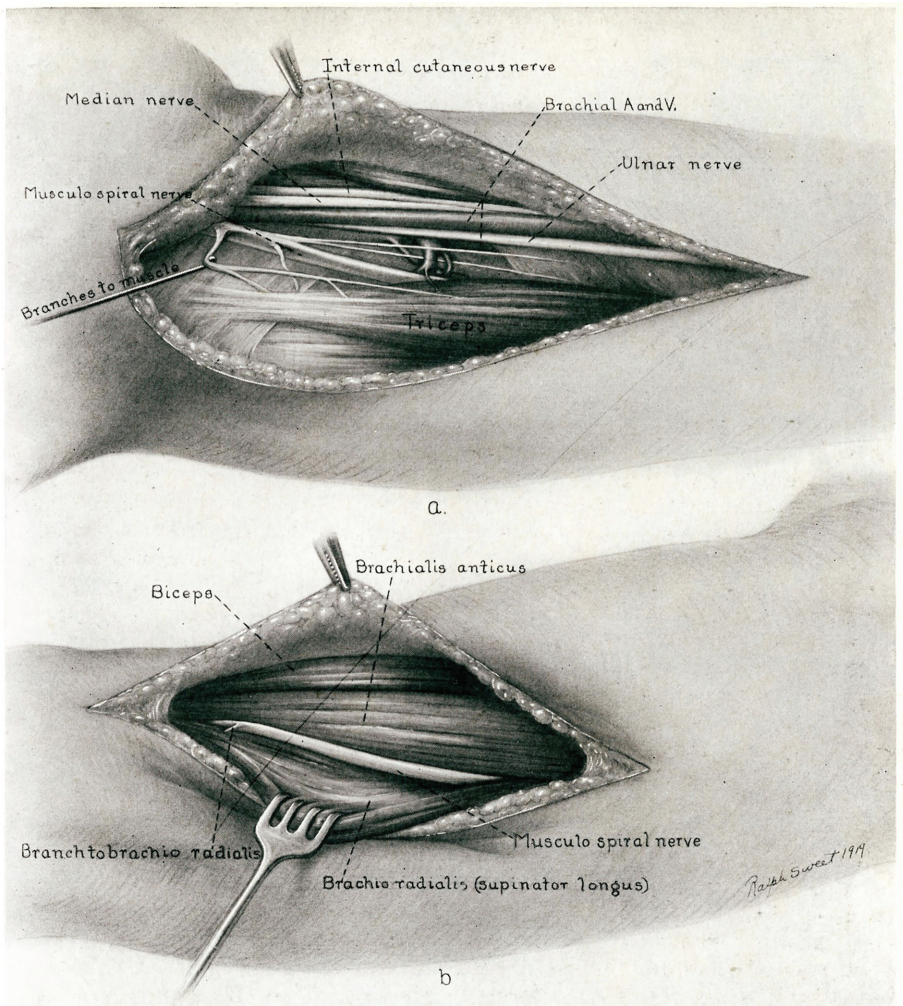


Fig. 3. Musculo spiral nerve. a, Transposed route, upper arm; b, transposed route, lower arm.



... With the fractures of the base, the bleeding from the ears, the later ecchymoses over mastoid, and the horseshoe ecchymoses from it around the auditory meatus attract attention to the fissures of the petrous bone. The bleeding from the nose or vomiting of swallowed blood, the ecchymoses, subpalpebral and subconjunctival, in the absence of direct injury to the soft tissues, are

important findings, and assist us in forming a judgment of the bone injury to the sphenoid, ethmoid, and orbital plates. Additional information may come from the character of other discharges from these orifices, from other ecchymoses, emphysema, etc. The roentgenograms help us less.

Such examinations and findings give information as to the severity of the trauma. Such one injury, however,

This page: illustrations by Ralph Sweet featured in "Methods to secure end-to-end suture of peripheral nerves" by Howard C. Naffziger, MD, Surgery, Gynecology & Obstetrics, 1921.

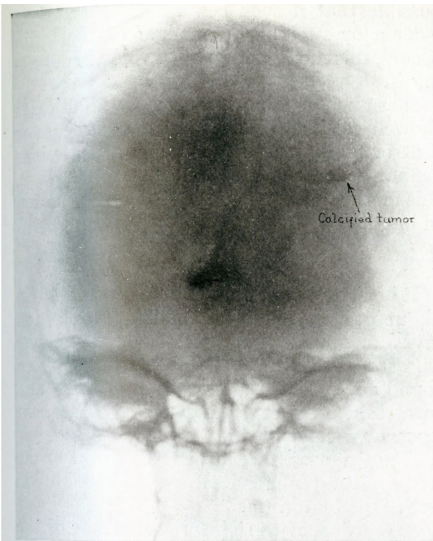
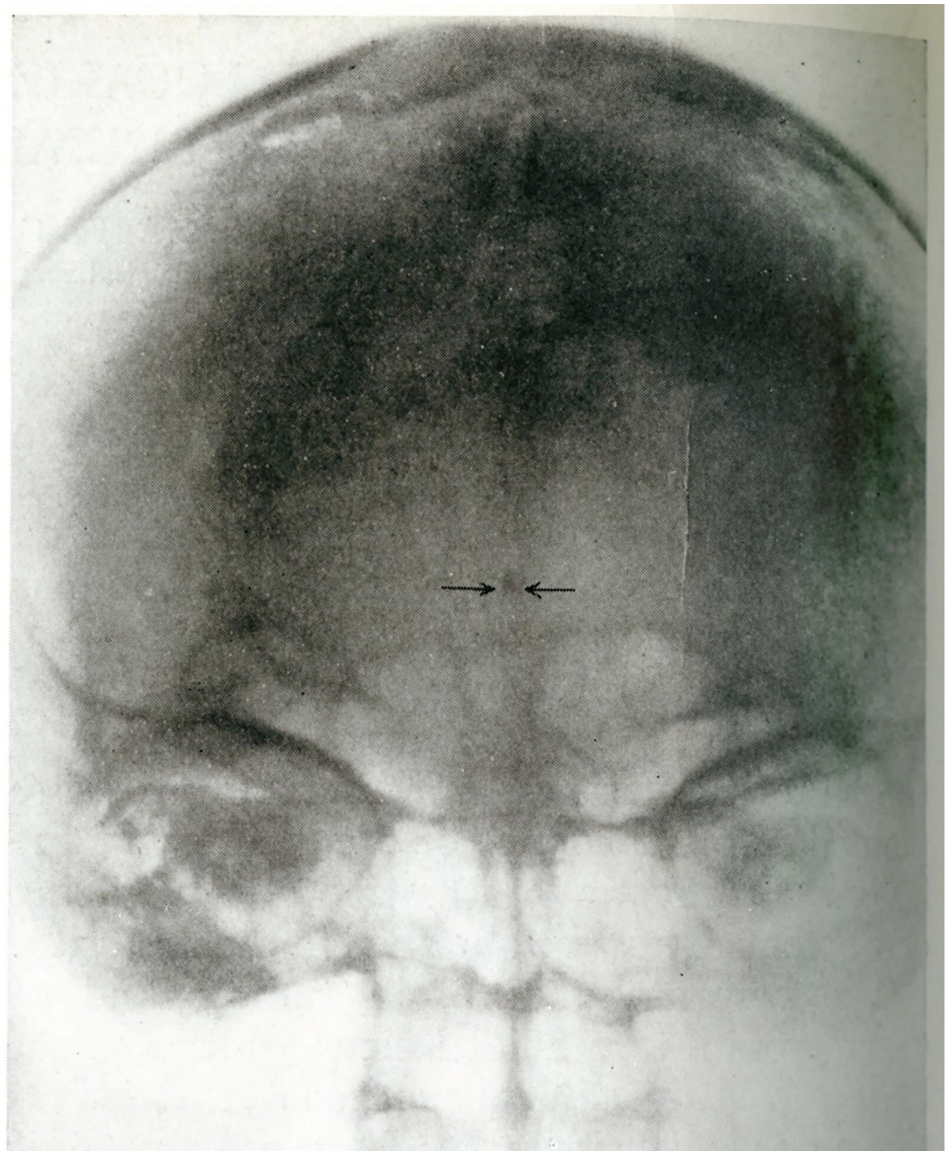


Fig. 4. Showing pineal shift away from the side of a calcified tumor.



Fig. 5. Marked shift of the pineal shadow.



bears little relation to the intracranial injury. The most severe brain injuries are often seen and later found to not be associated with any bone injury. A policeman's club may cause, by a sharp blow, a fracture without generalized brain contusion, where a thud of a sand-bag may widely disorganize the brain and yet produce no bone injury. Compression of a skull

between a ship's side and the pier may compress and fissure the skull widely and yet produce no brain injury. The type of trauma more often than the degree of bone injury is indicative of the brain damage. On the other hand, the bone injuries, particularly of the base, which may open avenues of infection to the meninges, are factors affecting our prognosis. 9

This page: images featured in "A method for the localization of brain tumors: The pineal shift" by Howard C. Naffziger, MD, Surgery, Gynecology & Obstetrics, 1925.



*Arnold D'Ancona,
Dean of Medicine at the
University of California
(1899-1912) and
Hospital Superintendant.
D'Ancona's support was
recruited by Naffziger
to establish a surgical
residency training program
emulating that pioneered
at Johns Hopkins by
Harvey Cushing.*

Developing Training Programs in the 1930s

The 1920s had been productive and pioneering. The fundamental strategy of bringing in good talent as residents to train in neurological surgery had paid off with results from creative collaborations yielding innovative clinical contributions to the field. With a well-honed team who had specialized training in neuropathology and surgery, Naffziger found himself in position to take neurological surgery to the next level. It was good timing. In 1929 Wallace Terry, the chairman of the Department of Surgery, announced his retirement, and Naffziger was selected for the position. It was the beginning of major institutional transformations in the university at large, and specifically for the place of neurological surgery at the University of California.

When Naffziger returned from his training at Johns Hopkins in 1912 and joined the UC faculty, the "affiliated colleges" of the University of California (the departments of medicine, dentistry, and pharmacy) had just been reorganized to become an integral part of the University under the designation of UC Colleges, and what had been known as the "department of medicine" would officially become the UC Medical School. A champion of this cause and advocate for higher standards in medical education was the Dean of Medicine, Abraham Arnold D'Ancona.

Also in 1912, Wallace Irvine Terry was appointed Chair of the Department of Surgery, a position he held until his retirement in



Doctors attending a lecture in Toland Hall. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.

1929. An avid traveler who spent time in Berne, Switzerland, and learned techniques of surgery on the thyroid and parathyroid glands from Theodore Kocher, thereby introducing the practice to San Francisco and laying the foundation for UC as a center for the treatment of goiter, Terry was a notable chairman for allowing specialties to pursue their own paths and mature with their own levels of autonomy from the general surgery department.

Throughout the 1920s, when Naffziger was steadily building a reputation as a skilled and innovative neurosurgeon and recruiting residents, Terry was supportive of the calls to find more hospital space for the stability and expansion of the mission of medical education. In 1920, Terry, in his dual role as Chair of the Department of Surgery as well as

acting Dean of the Medical School, wrote an annual report to the UC Office of the President where he underscored the importance of having access to the right number of hospital beds for successful medical instruction. His message was tethered to corollary concerns about the costs of hospital administration, tight university budgets, and the politics of treating different kinds of patients – namely, “private” versus “service,” or non-fee-paying, patients. Since the new University Hospital was constructed in 1917 with \$750,000 of local community support and private philanthropy, the questions of access to care and impulses to billable services would foreshadow pressures in university practice that would persist for decades.

“At least one hundred beds should be provided in order properly to teach sixty students. In the San Francisco Hospital the University has charge of forty-four beds in medicine. ... There are supposed to be forty beds set aside for the teaching of medicine at the University Hospital, but in the past six months there has been a steady decline in the number available for free or small-pay cases. The cost of the hospital maintenance has increased so formidably in the past two years that funds contributed by the University budget have proved more and more inadequate and the hospital has been forced more into private work until it is in danger of becoming essentially a private and not a teaching institution. ... The lack of stability and permanence of the University medical service stultifies any progressive scheme of departmental organization.”¹⁰

– Wallace Terry, MD, Chair of the Department of Surgery

The challenge of hospital space and managing costs for medical care was an administrative concern that would trickle from the top down, and eventually something that Naffziger would come to appreciate as he climbed up the administrative ranks.

The need for more teaching beds was already a particular concern for surgery. In 1919, the Department of Surgery (including neurological surgery) cared for 47% of the total number of hospital cases inclusive of service and private patients. But there was increasing curtailment of beds. In 1918, surgery had 59 beds assigned to it; in 1919, the number was 49. “Taken with the increase in the number of students,” Terry wrote, this “limits the amount of important bedside teaching of Surgery in this hospital and decreases the value of the house staff positions. The one great need in the Department of Surgery is more

teaching beds.”¹¹ Things were not improving throughout the decade.

The concern to make UC a leading school for medical education and training had dominated the philosophy of the college throughout the first three decades of the twentieth century. This institutional mentality impacted Naffziger and the development of neurological surgery in an important way: it provided Naffziger with the inherent support he needed to build his residency training program, allowing neurosurgery to crystallize as a unique specialty. On a more personal level, it may well have been the reason why Naffziger himself desired to learn more about the logistics of educational programs.

Naffziger summarized the general framework of neurological surgery education and training as it existed throughout the 1920s with the following:

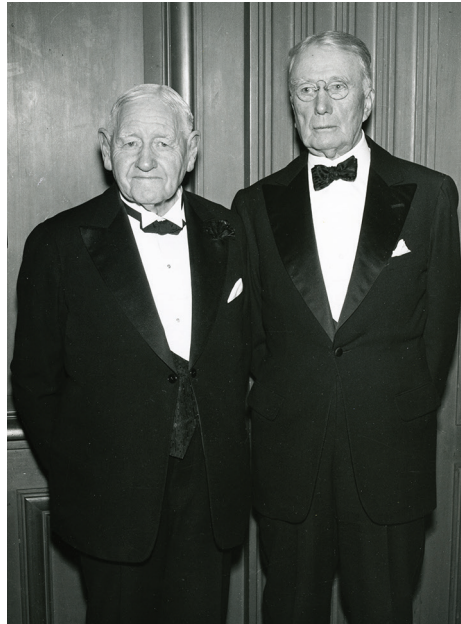


Photo of Wallace Irvine Terry (left) with Herbert C. Moffitt taken in late 1948. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.

☞ Neurosurgical teaching included much neurological teaching to second year students in physical diagnosis and class and ward work at the San Francisco Hospital. Fourth year weekly clinics and ward rounds with students continued. Referred work to the Out Patient Department add[ed] to the Hospital [had] built up so that by 1930 the service was a heavy one. Graduate or resident training began about 1920 an in addition to individuals specializing, other members of the resident staff in general surgery rotated through the service for six months at a time.¹² ☞

With increasing numbers of students and the aforementioned pressures on hospital space, there was a call to investigate strategies to see how other medical schools orchestrated clinical instruction. In 1927, Naffziger received a special request from the University of

California President, William Wallace Campbell. The president, Naffziger wrote, “asked me to visit such medical schools as I wished and to look into medical – particularly surgical – teaching and to submit suggestions for improvements in teaching in the UC Medical School. He was interested in the fact that the Mayo Clinic carried on [graduate] teaching in spite of the fact that all patients were private – no so-called service or teaching cases. I visited several schools and the Mayo Clinic. At the Medical Schools there were no striking differences in subject matter or distribution of time of the students as I recall. Bedside teaching and small groups were stressed (in conversations) and less lectures.”¹³

Medical student observing a surgical technique during the early twentieth century. During this time period, surgeons relied upon the availability of natural daylight in the operating room for both the operation itself, but also, to read X-ray slides mounted to nearby windows.

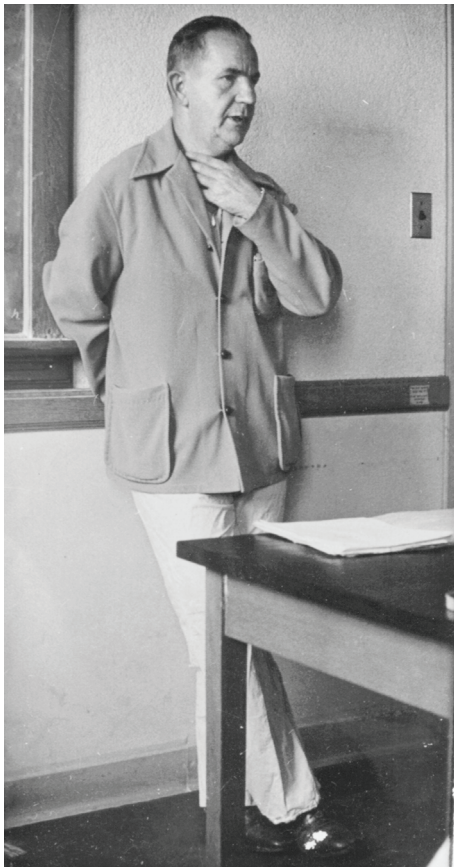


Naffziger prepared a detailed report of his findings, along with proposals for changes in the surgical training program. Through his own dedicated investigation, Naffziger suddenly found himself a leader in medical education. Two years later, when Wallace Terry stepped down as Chair of the Department of Surgery in preparation for retirement, the President appointed Naffziger as Terry's successor.

Immediately, Naffziger, along with the entire university administration, faced difficult times. The onset of the Great Depression tested the abilities of a medical school to perform capably, let alone expand. As the America Medical

Association reported in 1933, in the context of assessing developments in medical education and the costs of medical care, "medical schools, along with other institutions of higher learning, have struggled to exist. Almost without exception, income has been reduced and budgets have suffered accordingly. Salaries have been cut and faculty appointments terminated, entailing, in some instances, unparalleled hardship because, under existing circumstances, no other appointments were available. A few states have instituted a searching enquiry into the reasons for maintaining professional education at public expense." It went on to state that reports of a

committee investigating the costs of medical care and the methods of medical education issued “warnings of the dangers that must result if the production of doctors is not drastically curtailed.”¹⁴ In the face of pressures to reduce the number of medical graduates – from a study led by Willard Rappleye, former Professor of Hospital Administration at the University of California who was at this time Dean of the College of Physicians and Surgeons at Columbia – ideas of *expanding* a medical education program at a public university would have seemed daunting.¹⁵



Despite the challenges, as Chair of the Department of Surgery, Naffziger was now in a critical position to enact changes to the organization of surgery, which would, of course, profoundly affect the course of neurological surgery at UCSF, all together in terms of clinical service, teaching, and research. Among the most substantial developments in this regard that materialized in the 1930s was the creation of the modern residency training program in neurosurgery.

At the end of the 1920s, the full-time faculty in the division of neurological surgery consisted of Naffziger, Howard Fleming, Ottiwell Jones, and Howard Brown. Among Naffziger’s first acts as chair of surgery was to recruit an additional faculty member: Dr. H. Glenn Bell, an Ohio native who graduated from medical school at the University of Cincinnati and trained as a surgical resident under Mont Reid, who had trained under Halsted at Johns Hopkins. Bell moved to Southern California to start a surgical practice when Naffziger learned of Bell’s abilities from Reid and recruited him as associate professor of surgery and acting chief resident, a position he started in 1930. Bell’s remit: develop a surgical resident training program modeled after the one at Johns Hopkins.

Left. H. Glenn Bell, MD. Recruited by Naffziger to UC from Cincinnati, where Bell was trained in the Halstedian tradition by Mont Reid. Asked to build a formal residency training program, Bell became known as “the doctor’s doctor,” training hundreds of students, interns, and trainees in surgery until his retirement in 1960. He served as Chair of the Department of Surgery from 1946 until 1956.

Bell quickly proved his skills as a surgeon. He embraced and was responsible for introducing new technologies to the operating room. He arrived in San Francisco with a Bovie electrocautery unit that could coagulate small vessels. With it, Bell deftly dissected tissue with clarity and precision. Demonstrating his technique early on in front of the faculty, house staff, and local clinical surgeons, he began using the electrical machine in an operating room where highly volatile anesthetic was customarily used. Recalled a former student of Bell's who discussed this with him, "the observers were anticipating that the patient, surgeon, and entire operating suite would blow up or erupt in flames. Following the uneventful operation, Bell was summoned to Naffziger's office. As Bell admitted later, he was concerned that his academic career and appointment as chief of general surgery might be in jeopardy. Naffziger looked him straight in the eye and said: 'I think that coagulation unit is ideal for use in neurosurgical procedures. I would like to have that in the neurosurgical department, and perhaps you could order another one for your use in your department.'"¹⁶ The second unit arrived six months later.

Bell gained a reputation as

having a progressive approach to surgery that persistently and constructively challenged medical dogma. His was a personality type that complemented Naffziger's, and he garnered loyalty among trainees through new relationships and protocols of training he developed in surgery. He laid an important foundation that would make the kind of training program that he and Naffziger developed together possible.

Surgery involved high levels of commitment and thoroughness in preoperative, operative, and postoperative care. Above all, it required the efforts of a team. Preparing individuals to work within such an environment involved indoctrination and training that was open to different approaches. Naffziger and Bell asked fundamental questions of the process: "What is the goal that we seek for the men who put themselves in our hands?" "How broad should be his basic training?" In an era of specialization, the question was, in part, how much "broad knowledge and experience" should or could be acquired? A complicated question since even "general surgery" itself, said Naffziger and Bell, "is about as narrow as the other surgical fields." Proper training, as they saw it, avoided the pitfalls

of specialization where the rush to localize their knowledge created a medical practitioner who bypassed the necessary work to lay a foundation in disease etiology, pathology, and anatomy.

The recommendations they provide first addressed the need of

the teaching hospital to have the proper infrastructure to support a robust training program. This included funds for free beds and a departmental leadership that was committed to the wards and acting as supervisors and role models for young trainees.

The plan being developed at the University of California Medical School and Hospital is the so-called resident system or postgraduate school of surgery. Each man accepted for further training in surgery has had one or more years of instruction after graduation from medical school. We believe that it is preferable for him to have had an internship entirely on one service, for with the so-called general or rotating internship he is not on one service long enough to get acquainted with the work of his seniors, or for the instructors to learn his merits or special abilities. ... The man who desires to become a surgeon must have, aside from some technical skill with his hands, the ability to get along well with his associates, and to know how to approach and to handle his patients. The assistant residents are chosen after a searching interview to judge their personalities, their ideals, and their special fitness for further training.

They are started either on surgical pathology or research for a year. While on the pathology service they examine, in the gross and under the microscope, a thousand or more general surgical, gynecologic, and neurologic specimens, which are reviewed with the professor of pathology. They do, or see, all of the necropsies performed; last year there were 125 such cases. While the junior surgeon is on this service, he may examine the patient before operation and see him at the operating table, so that, when describing the pathologic process, the case is complete in his mind. It is most important that the young surgeon know

Excerpt from
Howard Naffziger
and H.G. Bell,
"The Postgraduate
Training of Students
in Surgery at
the University of
California," *Western
Journal of Surgery*
40 (1932), 384-389.

the fundamentals of pathology, for patients are coming under observation earlier in the course of disease, and pathologic processes are less advanced. The time spent in studying pathology is, perhaps, the most profitable of all.

The work in the research laboratory is carried out under supervision, but the young surgeon is given an opportunity to develop his initiative by work upon new problems or critical review of old ones. ...

After his training in pathology and research, he spends six months or longer on general surgery. During this time he takes full charge of the preoperative and postoperative care of his patients, always, however, under the supervision of the resident and visiting staff to whom he is responsible. He is first assistant at operation upon all of his patients and thereby is able to familiarize himself with different approaches, pathologic processes and technical procedures which he sees over and over.¹⁷ ... »

Naffziger and Bell went on to describe further activities in a training program that would all together last “five or six” years, including time at San Francisco Hospital where residents gain experience with acute abdominal and traumatic surgery, and out-patient clinics, while they continue to do research, present papers, and possibly publish. There was, according to the numbers of cases each year, enough opportunity between San Francisco Hospital and the UC Hospital for full training. In 1931, at the University Hospital alone, there were 4,872 surgical procedures. Of those, 1,185 were on private patients, leaving the

remaining 3,687 “teaching cases.”

While the nuts-and-bolts of the San Francisco program were spelled out, there was an overarching philosophy of the training program that would amount to something greater than the sum of the parts: their program was intended to build *character* and provide a grounding in investigations that would make surgeons *adaptable* to future progress.

The importance of the formal Surgical Residency Training Program at the UC Medical School is succinctly stated by Milton Chatton: It “had a profound effect on the entire health science center. He reorganized the program of didactic and bedside instruction.

Standards of medical and nursing services were improved. He succeeded in obtaining animal laboratories necessary for surgical training. He recognized the importance of applying basic science to clinical medicine and stimulated his students towards research. He developed a special section of anesthesia. He sought and obtained highly qualified residents to his attractive surgical training program."¹⁸

Needless to say, the training program had a profound impact on the development of neurological surgery at UC, forming a specialized residency program that in 1934 became the first in the west, and one of only a handful nationwide, to be recognized by the American Medical Association's Council on Medical Education and Hospitals as an approved site for residencies in specialties.¹⁹

Together, Naffziger and Bell recognized that surgical specialization was advancing the whole field of surgery in the United States, therefore stressing the importance of breadth of surgical training as a foundation for future development. Considering many different options for the most beneficial and rounded training, yet recognizing limitations of time and economy, the neurological surgery residency program – which started off as a one-year position, for one resident a year, who was paid between \$25 and \$75 a month – focused on pathologic processes and laboratory investigation.

By 1938, when Naffziger was President of the American College of Surgeons, he again commented on surgical training, this time with specific reference to neurological surgery, giving an account of the past few decades that had seen the creation of the specialty.



*University of California
Hospital, men's ward*

Quote from Howard Naffziger, "Content of Courses for Adequate Training in Neurological Surgery," *Bulletin of the American College of Surgeons* 24 (1939), 46-48.

“Increases in our understanding and treatment of surgical disorders of the nervous system have gone on apace and with increasing momentum in the last 50 years; in the last 25, the technical advances in surgical treatment have been hard pressed to permit the full utilization of our improved diagnostic methods and of the numerous and outstanding contributions to neurophysiology and neuropathology. The widest development of interest in this country had occurred in the last 20 years. Prior to the World War, with one or two notable exceptions, no one limited his activities to surgery of the nervous system. ... Whether we consider neurological surgery from the aspect of the seriousness of the conditions and the importance of the organs involved, or whether we consider its structure and the difficulties in diagnosis or the technical refinements required by surgical treatment, it is apparent at once that its demands are most exacting. That a person should practice such a surgical specialty without sufficient training in the general principles of surgery, such as are involved in the management of infection, shock, surgical emergencies, wound healing, and so on, is unthinkable. What general anatomy is to the orthopedist and the general surgeon, so is anatomy of the nervous system to the budding neurological surgeon. The training in neurology is, of course, essential to diagnosis. The general surgeon, who practices without a knowledge of surgical pathology, is in the same undesirable situation as the neurological surgeon who has no training in neuropathology. Surgery, neuro-anatomy, neurology, and neuropathology are linked inseparably.”²⁰”



Right: Aerial view of UC Medical Center before Moffitt Hospital was built.

This important moment in the history of neurosurgical training – and within the more general history of the evolution of residency programs as a whole – is necessarily implicated in the coeval debates about the utility and benefits of specialization at all. It was a debate that would not only impact the perceptions of specialist residency training programs, but the evolution of research projects, grant recruitment, and laboratory space, which was next on the horizon for the development of neurosurgery at the University of California, San Francisco.

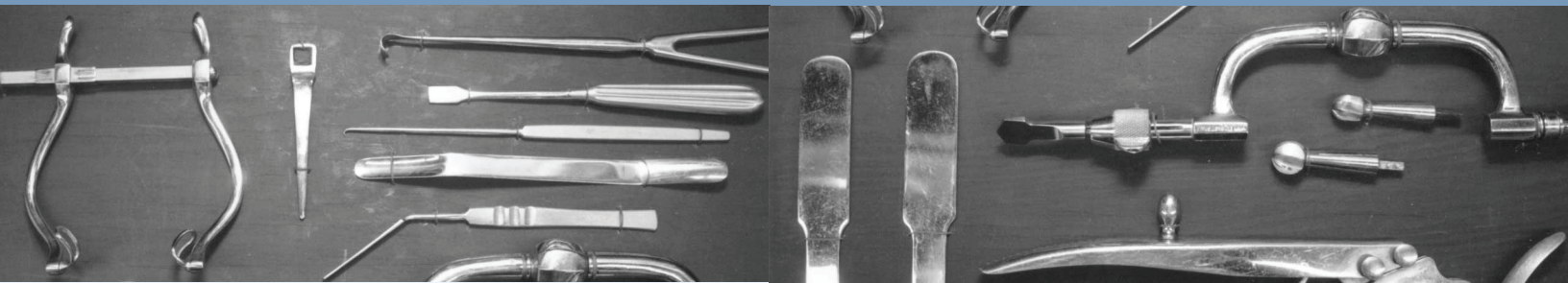
Endnotes

- 1 Cushing, Special Field Five years later, p. 335. Quoted in Samuel Greenblatt, "Harvey Cushing's Paradigmatic Contributions to Neurosurgery and the Evolution of His Thoughts about Specialization," *Bulletin of the History of Medicine* 77 (2003), 789-822.
- 2 "Report of the President of the University on Behalf of the Regents," *University of California Bulletin* 1921-1922 (University of California (System), Office of the President, 1922), Volume 16, p. 105. As we will see, throughout the 1920s until the 1960s, reference to neurological surgery (sometimes simply neurosurgery) is variously described as a "sub-department" (of the Department of Surgery),
- a "sub-division," a "division," and a "department;" however, it is important to note that these terms were literally interchangeable. In the 1950s, efforts were finally made to formalize the nomenclature of the organizational structure at UC, an effort that coincided with the formation of UCSF as its own UC campus with its own governance. The non-standardized terminology has led to confusion about the institutional status of neurological surgery in the early years, but – regardless of what it was called – what matters is the process by which it was financially and administratively governed, and its clinical, educational and research mission controlled independently. It is also worth noting that there was reference at this time to "sub-departments" of surgical pathology, anesthesiology, orthopedic surgery, and others.
- 3 Rosegay, (op. cit.), p. 795.
- 4 Howard Naffziger, "Brain Surgery with Special Reference to Exposure of the Brain Stem and Posterior Fossa, The Principle of Intracranial Decompression, and the Relief of Impactions in the Posterior Fossa," *Surgery, Gynecology, Obstetrics* 46 (1928), 241-248, *passim*.
- 5 Lissa Baird and Anil Nanda, "Surgery of the Posterior Cranial Fossa: Historical Aspects," in Anil Nanda, ed., *Principles of Posterior Fossa Surgery* (New York: Thieme Medical Publishing, 2012), chapter 1.
- 6 Howard Naffziger, "Brain surgery with special reference to exposures of the brain

- stem and posterior fossa: The principle of intracranial decompression and the relief of impactions in the posterior fossa," *Surgery Gynecology and Obstetrics* 46 (1928), 241-248.
- 7 Alexander Bunts, "The Disaster, 1929," in John D. Clough, ed., *To act as a unit: The story of the Cleveland Clinic* (Cleveland, OH: Cleveland Clinic Foundation, 2004), pp. 49-58.
- 8 Howard Naffziger, "Spinal Cord Tumors (Arachnoid Fibroblastomata)," *Surgical Clinics of North America* 2 (1922), 363-400.
- 9 Howard Naffziger, "Head Injuries: Indications for Surgical Treatment," *Surgical Clinics of North America* 3 (1923), 699-710, pp. 699-700.
- 10 *Annual Report of the President of the University on Behalf of the Regents to his Excellency the Governor of the State of California 1919-1920* (Berkeley: University of California Press, 1920), p. 146.
- 11 *Ibid*, p. 150.
- 12 UCSF Archives and Special Collections, Naffziger Archive, MSS 97-004 Box 1, Folder 2, p. 17.
- 13 UCSF Archives and Special Collections, Naffziger Archive, MSS 97-004 Box 1, Folder 2, p. 38.
- 14 The Council on Medical Education and Hospitals, "Medical Education in the United States and Canada," *JAMA* 101 (1933), 677-712, p. 678.
- 15 Harry Atkins, *The Dean: Willard C. Rappleye and the Evolution of American Medical Education* (New York: Josiah Macy Foundation, 1975).
- 16 Robert Albo, "H. Glenn Bell: The Epitome of a Surgeon," *Archives of Surgery* 140 (2005), 702-704.
- 17 Howard Naffziger and H.G. Bell, "The Postgraduate Training of Students in Surgery at the University of California," *Western Journal of Surgery* 40 (1932), 384-389.
- 18 Chatton, *Alumni Faculty Association Bulletin* (op. cit.), p. 10.
- 19 See *JAMA*, which started publishing lists on approved hospitals for residencies in specialties in 1933 (naming only one hospital, the Medical College of Virginia. In 1934, the total was six nationwide: UC Hospital, Presbyterian Hospital in Chicago, Boston City Hospital, Neurological Institute in New York, Strong Memorial and Rochester Municipal Hospitals in New York, and Medical College of Virginia.
- 20 Howard Naffziger, "Content of Courses for Adequate Training in Neurological Surgery," *Bulletin of the American College of Surgeons* 24 (1939), 46-48.

Chapter Three

The Emergence of a Neurological Research Culture



“*In a sense, I suppose, every medical graduate tends in time to particularize to a certain extent, and through liking or opportunity comes to be known as more expert or better informed than his fellows in one thing or another. ... Of all this there is no end or ever will be. For there are ways innumerable in science or practice in which we as individuals or groups of individuals come to particularize our work.*”¹

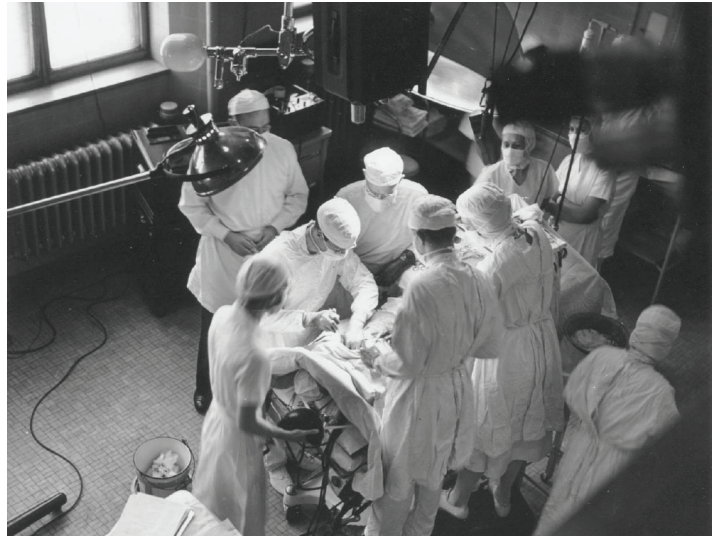
– Harvey Cushing (1920)

“*The tendency toward specialism often is decried. Nevertheless, while the present state of medical practice leaves much to be desired, and the specialist is too often a person of narrow vision and inadequate training, it is certain that specialization of effort goes hand in hand with progress.*”²

– Howard Naffziger and
H. Glenn Bell (1932)

In an address made in 1920 to the Tri-State District Medical Society at Waterloo, Iowa, Harvey Cushing reflected on the progress of neurosurgery since his last “accounting of stock” of the discipline in 1910, the year before Naffziger joined him as resident. In the address, he reflected on a certain inevitability of the trend towards specialization in medicine, and a rather critical attitude toward it amongst colleagues in the profession. Naffziger and H. Glenn Bell also recognized that there was skepticism that presented challenges to the idea of specialized training programs.

*Surgical team at
Johns Hopkins
in the 1940s*



But, like Cushing, who was such a strong model for their way of thinking about their profession, they held to the importance of keeping a footing in broader (“parental”) disciplines, like general surgery. As Cushing said, “shortcuts to specialization without thorough preparation in the fundamentals make incompetent if not dangerous practitioners, and so long as this is permitted within the profession itself we should be less intolerant of those who have smuggled themselves into the tree [medical practice] with no medical preparation whatsoever ...”³

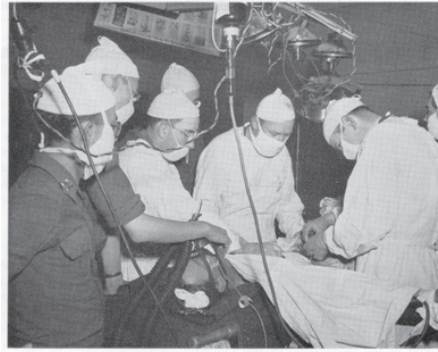
☾ It hardly seemed possible fifteen years ago that the surgery of the nervous system by itself could furnish material enough to occupy a surgeon’s undivided attention and insure him a livelihood, far less that it would promise opportunities within itself for further specialization on subjects like tumors of the brain in general or tumors of the pituitary body in particular. Time has shown, indeed, that these early misgivings were unfounded, and that there is not only an appeal but abundant opportunity for special workers who plan to restrict themselves to this outlying branch is evidenced by the fact that a number of surgeons interested in the nervous system have organized themselves into an interurban Neurological Society in the expectation thereby of making more rapid progress in this specialty through an intimate interchange of opinions made possible by clinical meetings.⁴ ☽

A Cautious Approach to Specialization

These concerns about the scope of activity and the professional identity of the neurological surgeon, from the leading practitioners of their time, might appear unnecessarily defensive. But their cautious approach pertained to the general perception about specialization in medicine. Sociologically, this was the beginning of an era when specialization was under attack as reductionist; medical practice was seen as becoming too mechanical, driven by too much technology – less holistic and patient-centered. Contemporary debates revolved around methodology in science, with the very ways that broad thinking and traits of an investigator's *character* informed and inspired possibilities of scientific inquiry. Consider, for example, the comments of Christian Herter, a neurologist, keen diagnostician of nervous diseases, and co-founder of the *Journal of Biological Chemistry*. A strong proponent of basic science research, he nevertheless also advocated "idealism and imagination" in science, arguing that no matter how particular the questions of research, scientific breakthroughs usually result from more roaming intellects, people with broad interests, justifying the foundation of disciplines in generalized activities.⁵ In the context of medical education and university life, concerns such as these regarding general versus specialized training loomed large.

In the process of specialization, where opportunities for yet further specialization present from within, the more particular the level of investigation, the more questions seem to emerge about neuropathology and the intricacies of bio-physiological processes that impact disorders of the nervous system. Thus, while throughout the 1910s and early 1920s neurosurgical publications like Naffziger's "clinical reports" may have been written in the mold of surgical instruction and technique with relatively little impact from laboratory work, the next decade saw a concerted turn toward more in-depth research.

This had started on the East Coast, notably with the founding of the Hunterian Laboratory of Experimental Medicine at Johns Hopkins by William Halsted and Cushing in 1905, and with the New York Neurological Institute (1910). Experimental research was further expanded with the founding of the Army Neuro-Surgical Laboratory, also at Johns Hopkins, by Lewis Weed in 1917, in recognition that 15% of casualties on the Western Front during the war sustained intercranial injuries.⁶ To illustrate the spirit of intellectual curiosity that drove basic-scientific research in neurological surgery, it is interesting to review Cushing's statement of the problems that were investigated to help shed light on underlying processes that lead to later manifestations of disease:



Surgeons at an evacuation hospital. Typically a unit was comprised of two general surgical teams, one orthopedic surgical team, one neurosurgical team, and one maxillofacial team. Battle casualties were often admitted at the rate of 100 to 150 per day.

“Granting that the choroid plexuses are the chief source of the cerebro-spinal fluid – and this has not been conclusively proved – is the process, as some believe, a transudation, or an actual secretion, or, as Mestrezat regards it, a mere dialyzation from the blood? What conditions activate, and what conditions inhibit these choroidal glands? Have they an internal as well as an external secretion? To what primary diseases are they subject? How early in embryonal life do they secrete? Why does the fluid which they elaborate differ so greatly from that secreted by most other glands? Why are the cells so impermeable to the passage from the blood stream of drugs and of substances such as the bile pigments which, in conditions of jaundice, quickly stain all other body tissues and fluids?”

Investigations led to subsequent publications that began to answer some of these questions, suggesting (for instance) that the withdrawal of cerebrospinal fluid during a suitable experimental septicemia resulted inevitably in the production of meningitis.

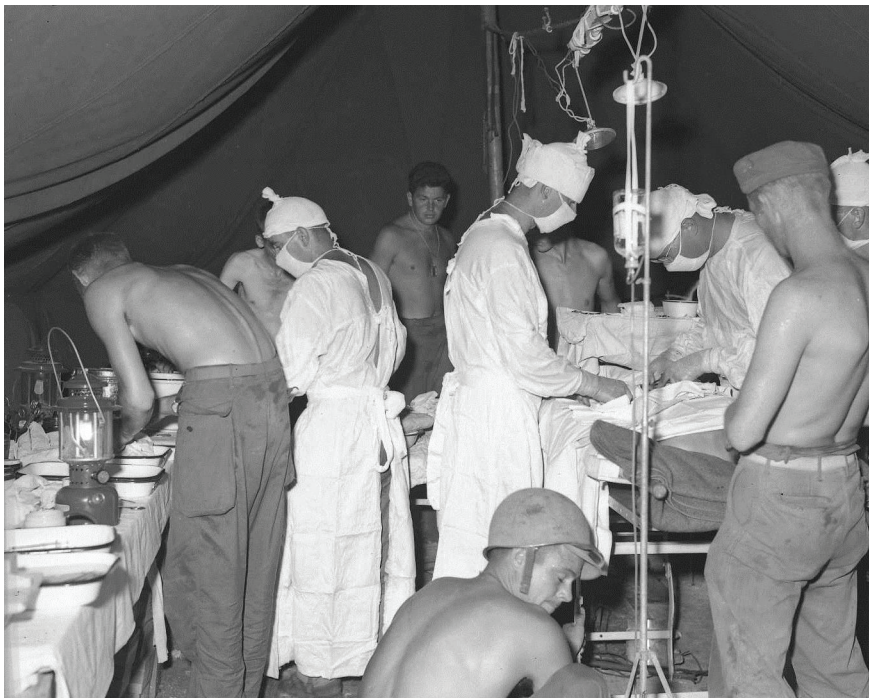
It was in the spirit of the quest to find answers to these sorts of underlying questions that the specialty of neurological surgery grew more research oriented. Already historically engaged with training and collaborations with East Coast colleagues, and having been there on the Western Front with Harvey Cushing to see first-hand the necessity of probing deeper into neurological disorders, it was unquestionable for Naffziger that the next step in developing neurological surgery at the University of California would be to concentrate on developing

a more robust research agenda. Having succeeded in defining the specialty of neurological surgery at UC through clinical service and training programs, he began to put his effort into establishing laboratory space and grant recruitment.

Just before Naffziger became Chair of the Department of Surgery in 1929, a few important developments occurred that profoundly impacted future plans for the medical school and for the opportunities to develop neurological surgery at the University of California.

In 1926 the President of the University of California and the Regents deliberated whether to

keep the medical school in San Francisco or move instruction to Berkeley, thus consolidating all departments of the university in one place. This topic had been debated for more than a decade (and, as we will see, was for decades to come), and stemmed from the fact that the basic science departments and labs that were associated with the medical school had been moved to Berkeley as an emergency measure following the earthquake of 1906. In 1913, the dean of the medical school, Arnold D'Ancona, wrote a statement to the President and Regents summarizing the challenges this had presented:



Left: World War II field hospital. Learning that 15% of casualties in WWI were caused by intercranial injuries, neurological surgeons became an important part of Auxiliary Surgical Groups (ASGs) such as this deployed in WWII. Image courtesy of National Museum of Health and Medicine #D45-416-68B

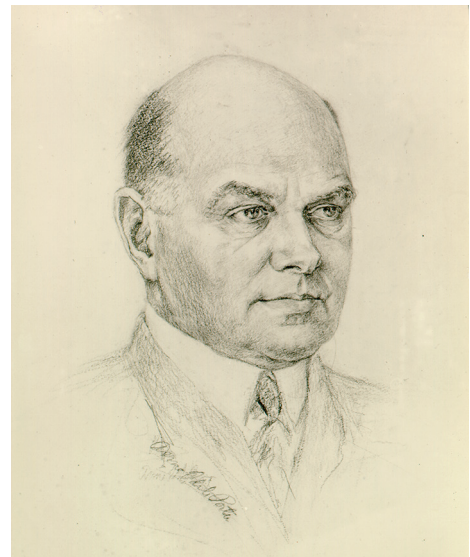
“After the earthquake and fire of 1906, the need for a space for a hospital wholly controlled by the university made necessary the separation of the work of the first two and of the last two years [of training] in medicine. It became necessary to transfer the departments of anatomy, physiology, and pathology to Berkeley, while the clinical subjects were still conducted in San Francisco. The separation made an unnatural division injurious to both parts. The board of regents has determined that ultimately all departments of the college shall be grouped together and in San Francisco. If the clinical departments were maintained in Berkeley, the fundamental sciences of physiology and pathology would have the advantage of a close alliance with physics and chemistry, anatomy would profit by association with biology, while the clinical departments would have the inspiration of an academic atmosphere. These advantages, however, seem to be outweighed by the varied clinical opportunities afforded by a metropolitan community.”

R. Langley Porter was appointed Dean of the UC Medical School in 1927. A strong advocate of a well-rounded medical education, he oversaw the return of the divisions of basic sciences back to San Francisco which had been relocated to Berkeley after the 1906 earthquake. He retired in 1940.

Now thirteen years later, the Regents finally passed a resolution that would secure the future of the health sciences campus in San Francisco, establishing science departments there, and gradually providing that campus with more autonomy. It promptly meant leadership reorganization.

The first important act here was the appointment of R. Langley Porter as Dean of the Medical School. The Dean's office had somewhat languished throughout the 1920s. Since Herbert Moffitt's retirement in 1919, interim deans had held the office, uncertain of the future. Now, Porter was invested with authority to

examine the school's structure and curriculum, which he described upon his appointment as “a disintegrated institution.” Part of





Langley Porter Clinic (image from the 1960s), later named the Neuropsychiatric Institute. Established during difficult economic times of the Great Depression, showing Dean Porter's commitment to clinical expansion at UC and support of the neurosciences.

Porter's reform initiative led to Naffziger's previously discussed tour of medical schools to survey curricula, as well as to the eventual construction at Parnassus of the Clinics Building and the creation of the Langley Porter Clinic, later the Neuropsychiatric Institute (with support from the California Department of Mental Hygiene).

The second significant event was the 1926 gubernatorial election that passed proposition 10 for "Bonds for State Buildings and University Buildings," thereby raising \$8,500,000 in state bonds for the erection and maintenance of state buildings at the capitol and

university buildings in Berkeley and Los Angeles.⁸ This was a major boost to university planning.

The building initiative was a development that caught Naffziger's attention, and gave rise to an idea specific to making neurological surgery competitive nation-wide. Naffziger articulated a vision of establishing a neurosurgical institute along the lines already established at Johns Hopkins. In 1926, Naffziger wrote a compelling letter to Chair of Surgery Terry presenting his argument.

Proposal for Western Neurological Institute at the University of California Medical School

Dear Doctor Terry:

Neurological surgery as a highly specialized branch of surgery is covering an increasingly large field. It merits, and in its development it is receiving, a large share of attention at the medical schools of Harvard, Johns Hopkins, University of Pennsylvania, Columbia, University of Michigan, Washington University and the Mayo Foundation.

The University of California Medical School has been the first in the west to give special attention to surgery of the nervous system. The development of this branch should proceed along with neurology. To this end special facilities are necessary. A close union should be retained however, with other branches of medicine.

For progress in this line a neurological institute is highly desirable, wherein individuals with neurological disorders both medical and surgical may receive study and treatment. There is no such institute in the west. There is a decided need for it in this section of the country and its beginning should logically be in the University of California Medical School. Such an institute should include beds for the care of both clinic and pay cases. As full time members of the staff, a neuropathologist and

an experimental surgeon or physiologist should be among the first considerations.

Upon the settlement of policies regarding the future development of the school, it would be desirable to raise sufficient funds to furnish endowment for such salaries. I believe such salaries can be maintained without help from the University.

Regarding beds - the more free beds available, the greater will be the opportunities. With only a few available as at present, this number can be supplemented by providing facilities for the handling of acute injuries, head injuries, fractured skulls, fractured spines with paralysis and nerve injuries. These cases can be obtained in considerable number providing the ward rates for such cases are not in excess of rates given in other hospitals. At present our rates are in excess and this prevents the filling of beds which could be used for a limited amount of instruction.

It is not beyond the possibilities to establish a relationship with other state institutions, viz - the various insane hospitals, schools of reform, home for feeble minded and epileptics and even prisons, so that beds in the neurological institute would be available for the treatment of special cases from such institutions.

“The entire field of research is now open and relatively new in the field of neurological surgery that it is reasonable to expect great advances in the future.”

The entire field of research is now open and relatively new in the field of neurological surgery that it is reasonable to expect great advances in the future. Neurological surgery has been for ten years one of the most productive fields of medicine.

As a beginning in the establishment of such an institute, the following possibility is suggested.

With the program of building now possible for the University in light of the recent election there might be an opportunity to house the contents of the Hearst Anthropological Museum in Berkeley. The present building is of stone and brick. It can be readily connected with the third floor of the University Hospital by a closed corridor. In the interior, alteration of partitions, the installation of an elevator and additional plumbing would be required. These would not I think, be a very great expense. I have obtained no figures but I should think that twenty-five to thirty-five thousand dollars would put the building in condition to house at least thirty patients and possibly forty. Such an addition to the bed capacity of the University plant could be effected without alternations in methods of administration. The present admitting and business office, the kitchens, X-ray, operating rooms, etc are adequate for such an addition. The heating plant is I understand, not capable of expansion. In that event the installation of a separate unit would not be a great undertaking.

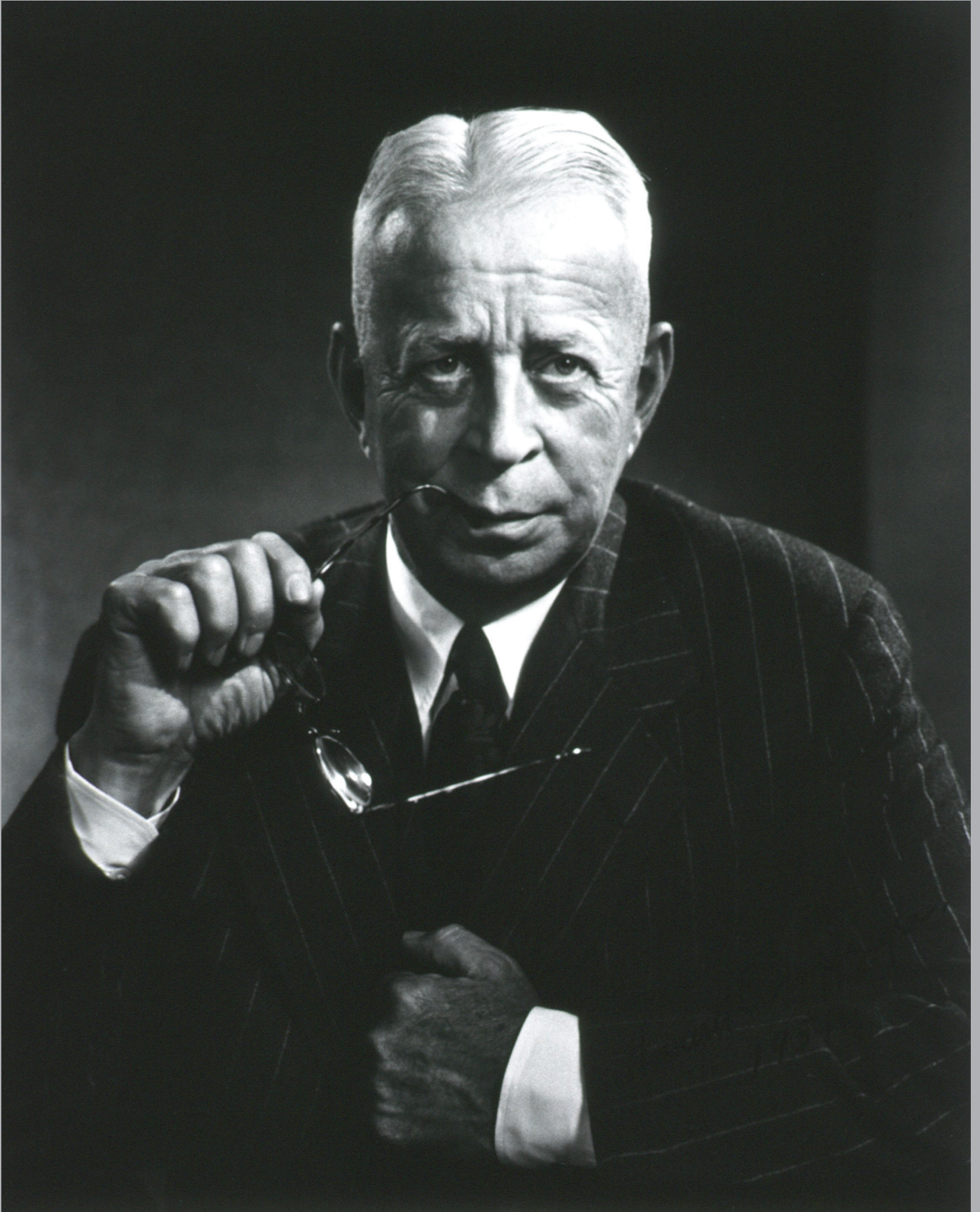
“Neurological surgery has been for ten years one of the most productive fields of medicine.”

Any beds in this building which are unfilled by neurological and neurosurgical cases can be readily taken over by other “head specialties,” viz – eye and ear, nose and throat, as these separate departments speak urgently of their desires for beds. Such an arrangement could function during the development of the institute and the accumulation of an adequate endowment.

There is reason to believe that the establishment of a western neurological institute can not be far off as there is no place of its type on this coast. It is my desire to have such an institution developed in connection with the University of California Medical School to which I believe it would be a strong and a productive addition, and serve a wide felt need.

Very truly yours,

Howard C. Naffziger



Naffziger's proposal, which demonstrates characteristic initiative and gumption, arrived at a time when not only the University, but Terry himself, had a lot on his plate. Approaching retirement, nothing immediately would happen with Naffziger's proposal. But when Dean Porter appointed Naffziger to succeed Terry as Chair of the Department of Surgery, new opportunities arose to pursue a research agenda.

If the 1930s were primarily about continuing advances in surgical technique and innovations in resident training, the 1940s were about laying the foundation for neurosurgical research, something that Naffziger would become passionate about as neurological surgery grew at UC.

By the beginning of the 1940s, Naffziger's reputation had grown in the ranks of the profession. In 1938, he became president of the American College of Surgeons, where, as we saw earlier, he advocated well-rounded, laboratory-based training for neurosurgeons. In 1940, he was chair of a committee that established the American Board of Neurological Surgeons, and he served as chairman of that Board until 1949.

In 1944, Naffziger turned 60. He received his MD from the University of California 35 years earlier, and had been a member of the faculty for 32 years. To celebrate his 60th birthday, the *Journal of Nervous and Mental*

Disease honored Naffziger by publishing salutations from Francis Scott Smyth, the Dean of the Medical School, and Robert Sproul, President of UC, who referred to him as "one of the most distinguished brain surgeons in the country." Robert Foster Kennedy, the controversial British-trained neurologist who was professor of neurology at Cornell, wrote of Naffziger's achievements in bringing neurosurgical science up to the standards previously associated with the East Coast. "For too long, the eastern seaboard was inclined to regard itself as the lantern-bearer of scientific thought," wrote Kennedy. "But the West has been called in to redress the balance of the East, and in the early Life Work of Howard Naffziger, that is, in his first sixty years, we see the formation, in California, of a school of neurological surgery; and even more importantly, a school of thought in neurological surgery."⁹ The rise to prominence of neurosurgery in San Francisco, however, is also attributed to the faculty recruits that Naffziger oversaw as Chair of Surgery over the previous decade.

Opposite: Howard Naffziger, 1951. Image courtesy of the National Library of Medicine.



Robert Burns Aird, founder of the Department of Neurology at the University of California Medical School, and established the path of a long-term relationship with the Department of Neurological Surgery.

The Rise of Neurosurgical Research

One of Naffziger's early faculty recruits when he was chair was Robert Aird, enticed to San Francisco from the University of Rochester in 1932 with the general remit to "do research." "Recruit" is a somewhat misleading term since, as Aird was to discover a few years later, his monthly stipend of \$100 was paid out of Naffziger's own pocket. This may possibly have been a result of there not being any non-clinical, full-time, research positions in the medical school, and thereby a difficult appointment to make official, especially with severe budget cutbacks. It was certainly an indication, however, of Naffziger's commitment to start a surgical laboratory and bring basic science to his department.

Aird was turned on to the field

of neurology while a medical student at Harvard where he studied with Walter Cannon, Harvey Cushing, Stanley Cobb, and William Lennox. He interned at the Strong Memorial Hospital in Rochester, working closely with neurosurgeon William P. Van Wagenen, Cushing's disciple. While stimulated by the field, Aird harbored a hesitation to follow so closely his father's steps, John William Aird, who graduated from the Medical Department of the University of California in 1893, and had a busy clinical practice in Utah, his native state. But however interesting neurological surgery was for Robert Aird, his interest in other areas of science pulled him away from the clinic and towards the laboratory. As he explained:

“Most of the work in the 1920s and 1930s was on brain tumors, and they were usually advanced cases. Although I was able to do it and Van tried to hold on to me, I finally decided that the real challenge was research. The main reason for this was my premedical training in physics and chemistry. I had seriously considered going into physics, and throughout my medical training I had followed its scientific aspects in physiology, biochemistry, pharmacology, and so on with great interest. I was conscious of new advances of science in electronics and chemistry, and realized the great promise of their application in medicine. This seemed especially promising to me in neurology, which had been held back by its great complexity and the fact that the techniques used successfully in other systems, such as in cardiology and the G-I system, had proved inadequate for the more delicate nervous system. The neurosurgeons were a fine group and doing the best they could, but research was the great need. The new techniques which made this possible had just been developed, and this seemed to me to be the great challenge and the promising course to follow.”¹⁰

Naffziger agreed. Aird arrived to find research plans truly in the epitome of “development.” The laboratory had essentially no equipment, and there were no research funds. Aird planned to work on recording sensory impulses of large nerves from different organs as they fed into the central nervous system measuring electric currents with a shielded needle. This was a few years before electroencephalography entered the scene in 1934-1935. However, nowhere at the University of California was there a cathode-ray oscilloscope.

“I just couldn’t believe it!” said Aird. Instead of this project, therefore, Naffziger suggested he work on a project of particular interest to him that also intersected the clinical and surgical care of patients with malignant exophthalmos. Naffziger had devised an operation to relieve the pressure on the eye in the orbital cavity caused by the hypertrophy of the extraocular muscles in advanced cases of malignant exophthalmos. Clinically, the problem was associated with thyroid function abnormalities, and Naffziger had obtained pituitary hormones from Herbert Evans, director of the Institute for Experimental Biology at Berkeley, in order to further research the problem. Using guinea pigs, Aird discovered the role of thyrotropic hormone and published on it.¹² “Naff was delighted,” said Aird, “Evans was delighted; I was beginning to prove myself.”

Anna Koeller and James O. Culver working in a laboratory at Langley Porter Clinic 1943. Image courtesy of San Francisco Public Library Historic Collection.



The links with the Berkeley lab gave Aird further ideas about establishing collaborative research projects with Berkeley science departments, including a study of blood and cerebrospinal fluid magnesium and calcium in epilepsy using radioactive isotopes, and pneumoencephalograms to study the blood-brain barrier at the UC Hospital. This would prove important for future developments in neurosurgical as well as neurological research.

In 1941, the California state legislature enabled the Department of Mental Hygiene to establish a neuropsychiatric institute at UC to train doctors for the state asylums. Many specialties were involved, including an EEG lab,

which Aird directed. For the neurosurgical ward, Naffziger recruited Edwin Boldrey, a medical graduate from Indiana who had neurosurgical training at the Montreal Neurological Institute where he worked with William V. Cone and Wilder Penfield. His research was on somatic motor and sensory representation in the human cerebral cortex. Another specialty was psychiatry, at that time a division of the Department of Medicine, Chaired by William Kerr. Various accounts suggest that Kerr and Naffziger were not on the most amicable terms, with Kerr suspecting that Naffziger was maneuvering to take over neurology, which was also a division of medicine at the time.



Edwin Boldrey, MD

Additional logistical problems in organizing the neuropsychiatric institute – the full plan of which was never fully articulated in the legislation – meant that what might have led to a collaborative clinic instead in effect became the Department of Psychiatry. Boldrey was transferred to run the neurosurgical service at UC Hospital.

Boldrey was involved in a wide range of research topics, becoming an author on 116 scientific papers as a result, including collaborative work on epilepsy, brain abscesses, arteriovenous malformations, and the surgical, radiation, and chemical therapy of brain tumors. More in-depth research for which he became well known included his use of

stereoscopic cerebral angiography, hypothermia for intracranial surgery, and anterior cervical disectomy without fusion.¹³

Boldrey was also a skilled and respected surgeon, and when operating on a patient with a malignant melanoma is said to have been the first surgeon to successfully perform total excision of the pituitary gland. In 1948, he was author on a report of a committee to assess the condition of operating rooms at UC Hospital. The report's summary and recommendations provide interesting insights to the operating room conditions in the 1940s:



“ The general morale and inattention to finesse of technique throughout the entire operating room suite are greatly deplored. This is found existing to some extent in each group which regularly works on the operating room floor. It is strongly recommended that closer attention by surgeons and operating room nurses be paid toward preserving complete aseptic technique at all times and calling all breaks in technique to the attention of the person responsible and the necessity for taking adequate means of correction of breaks in technique should be emphasized. Sources of contamination through opened windows scarcely twenty feet above a windy street, open doors between the regular hospital corridors and the operating rooms and scant attention to the passage of unsterile clothing through, about and around the operating suite and the ‘sterile field’ are only a few of the points which been receiving less and less serious attention by surgical personnel.”

– Report of Subcommittee on Operating Room Suite
at UC Hospital (1948)

Another arrival on the neurological surgery scene in the 1940s was Bertram Feinstein, who joined in 1947. Feinstein (who was married to politician Dianne Feinstein from 1962 until his death of colon cancer in 1978) was an experimental neurologist who studied muscle functions in relation to locomotion before heading to Sweden in the early 1950s to learn the techniques of stereotaxic neurosurgery with Lars Leksell, developer of the stereotactic (or “Leksell”) frame, an arc-quadrant instrument that used three polar coordinates (angle-depth-and anterior/posterior location) to target structures of interest for precise surgical

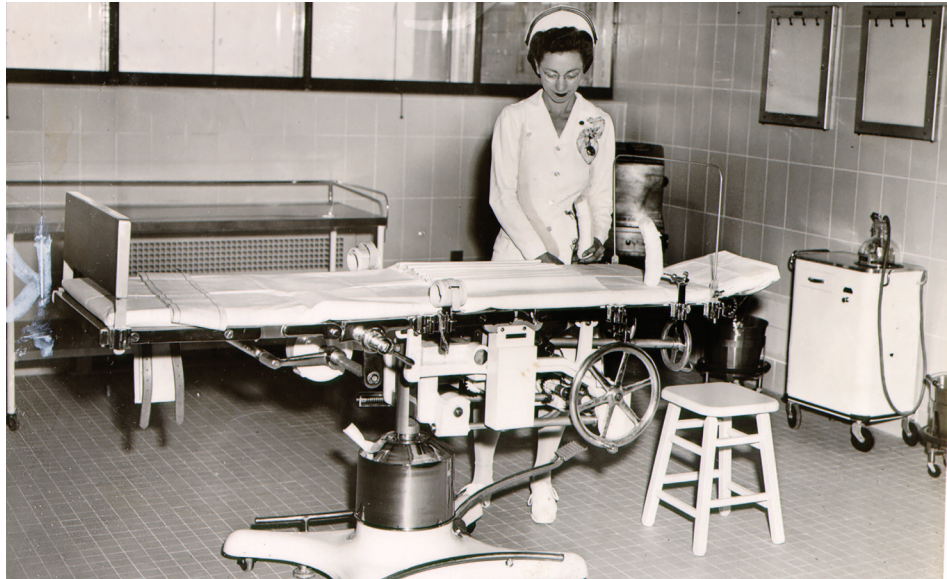
intervention. Feinstein is reported to have introduced the use of the device in San Francisco, where it became part of clinical use at the Langley Porter Clinic and later Mt. Zion Hospital, and developed into an important area of surgical research for the Department of Neurological Surgery.¹⁵

In 1946 a new neurosurgical resident arrived. John Adams received his medical degree from Harvard and was inspired by the work of Frank Ingraham, Neurosurgeon-in-Chief at Boston Children’s Hospital. On his way to active military duty in 1941, Adams, originally from California, asked Ingraham for



A photo of John Adams addressed to him from Leo M. Davidoff. Davidoff, like Howard Naffziger, trained in neurosurgery under the direction of Harvey Cushing.

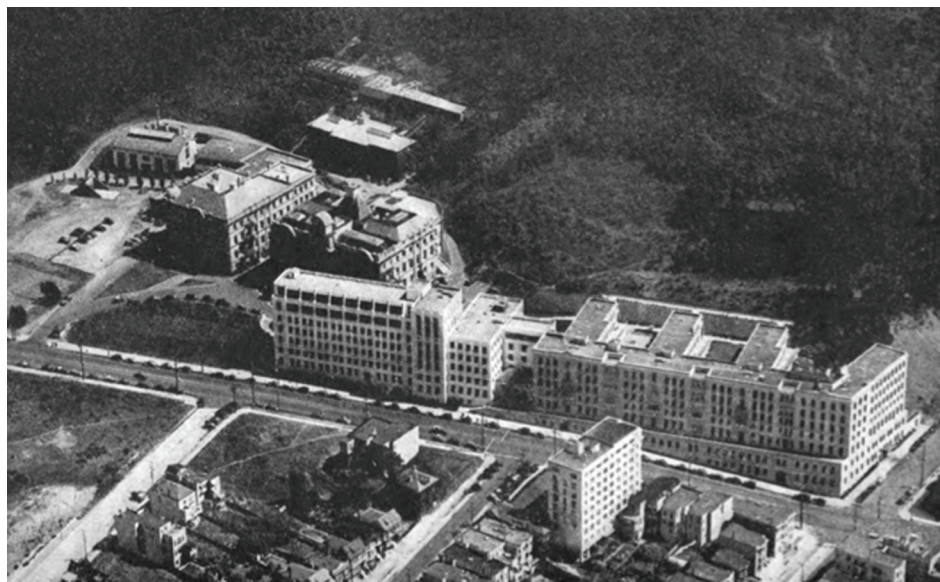
Surgical Nurse Marie Callori checking equipment in an operating room at Langley Porter Clinic, 1943. Photo courtesy of the San Francisco Public Library Historic Photo Collection.



advice about pursuing a career in neurosurgery, and expressed an interest in the Montreal Neurological Institute. Ingraham replied: "Why would you want to go to Montreal when you have Dr. Naffziger in San Francisco?"¹⁶ As soon as his tour of duty was complete, in January 1946, Adams arrived in San Francisco.

At this time, neurosurgery was allocated 22 beds in the 250-bed UC Hospital, which was under the division's capacity. Adams noted that it was a service that required as many as 35-40 beds when they could be borrowed from other services. In an autobiographical account written years later, Adams summarized the practice when he arrived:

“*The neurosurgical practice was very similar to that at other major centers. In addition, a large number of patients with severe essential hypertension were treated with bilateral combined thoracolumbar sympathectomy and splanchnicectomy (Smithwick procedure) done in two stages, 8-10 days apart. The standard general anesthesia for neurosurgical operations at UCSF was rectal avertin followed by nitrous oxide without intratracheal intubation. As might be imagined, if the pleura was torn during the thoracic exposure – which occurred not too infrequently – both the operative procedure and anesthesia became difficult. This often resulted in interesting comments from both the surgeon and the anesthetist.*”¹⁷



The Medical Center at the University of California, San Francisco circa 1945. Photo courtesy of the University of California Bulletin for the School of Pharmacy (1945).

1947: Departmental Reorganization

Toward the end of the 1940s, the plans to build the UC Medical School into its own campus, with science departments and new buildings, was now a twenty-year consideration that was moving very slowly. Throughout that time, particularly under the deanship of Langley Porter, departments were given more autonomy and many chairs encouraged the development of specialties, in turn giving divisions more flexibility to control their affairs. This was the case with surgery under the chairship of Naffziger.

In 1947, Naffziger was 63 years old, four years away from mandatory retirement. It has often been reported that this year saw the creation of the Department of Neurological Surgery with Naffziger as its first chair.

Naffziger himself states this in his autobiographical notes, though slightly misremembering the date: “In 1948 at my request I was relieved of the Chairmanship of Surgery and appointed Professor of Neurological Surgery with a separate department.”¹⁸ There is some truth to this, but a more sensitive historical understanding of the circumstances will help illuminate a series of events later in the department’s life.

In the 1940s, with the relationship between the UC Medical School and the campus at Berkeley still being worked out, the University of California did not have a standardized nomenclature or procedure for defining or establishing “departments.” The structure and relationship between different administrative offices – from the state-appointed governing Regents, to the UC Office of the President, to the Deans of the Colleges, to Department Chairs,

Operating room in the Herbert C. Moffitt Hospital and Medical Sciences Building at UC Medical Center, 1955. Image courtesy of the San Francisco Public Library Historic Photo Collection.



to Division Chairs, to Professors of Hospital Administration – were loosely defined. Even the term “School” and “College” were used somewhat interchangeably. When Langley Porter was appointed Dean in 1927, the UC President made it clear that all matters involving the governance of the Medical School would flow through the Dean’s office, and that Porter would be the sole liaison with the President’s office, thereby in effect giving Dean Porter more control to administer and build his School as he saw fit. But throughout the period and throughout the 1950s the President’s office still “officially” made professorship appointments through issuing letters and accounting for them in state legislated reports to the governor.

There appears to be no extant file in the archives of the Office of the President or the office of the Dean of the Medical School reflecting a University, or Regentially, sanctioned allocation for a new “Department.” However, it is clear from correspondence that Naffziger was, in 1947, appointed

“Professor of Neurological Surgery.” That same correspondence, however, throughout the following few years, well into the 1950s, refers to him as chair of the *division*, as well as the *department*, of Neurological Surgery, both in terms of how Naffziger signed his letters and how the Dean or President addressed him. The words department, division, and even sub-department, were used interchangeably – the latter probably referring to a “sub-department” of the “Department of Medicine,” for those with institutional memory recollecting when the entire medical school was a department of UC. The fact is it would take decades for the institution to formalize and standardize the procedures for establishing school and departmental (as well as medical center and campus) organization.

A further statement in the archives of the UC President’s office shows moves toward a resolution of this matter. In 1955, the University was in the midst of focused discussions (again) about whether to consolidate



Partial scene from a 1937 mural by Bernard Baruch Zakheim, a student of Diego Rivera's, depicting the history of medicine in California. This scene shows H. Glenn Bell performing surgery in the left center foreground.

UC on the Berkeley campus or provide San Francisco with its own complement of departments to round off the necessary disciplines to provide thorough training in the health sciences. Titled "A plan of organization for the basic medical sciences," which was a report prepared for the president, it assessed the following possibility: "Place in a single department under the leadership of a departmental chairman, all the activities in a given basic medical science now being sponsored independently by the several schools and colleges." It also looked at administrative language. "The semantic aspects of the terminology used have been thoroughly investigated. We believe that the Medical Center should be officially designated 'University of California, San Francisco,' a term in keeping with all other campuses. The word 'Division' is used in many ways throughout the University, ranging from an entire segment of the whole university to a portion of a department. It seemed more fitting than the designation 'group.' The term 'school' was rejected for

reasons mentioned above (though it should be applied to the four professional schools in lieu of the designation 'college,' in this Committee's opinion)." Ultimately, with the creation of science departments in San Francisco including anatomy, microbiology, pathology, pharmacology, and physiology, neurosurgery would take on its modern departmental form, with the appellation "department" used in the way we understand it today.

Another consideration that sheds light on an interesting dimension to the department's history may also have impacted the decision to put Naffziger in charge of an autonomous division or department of neurosurgery in 1947, putting aside the accolade this amounted to in respect of his distinguished career at the university. Throughout his time at UC, Naffziger, along with colleagues including Ottiwell Jones, Howard Fleming (until his early retirement in 1943), Eugene M. Webb, and Howard A. Brown had a private neurosurgical practice in downtown San Francisco. Edwin Boldrey and John Adams were also

part of what was referred to as the downtown “firm” until Adams left the practice in 1951.¹⁹ Much of the departmental correspondence in the late 1940s and 1950s was written on letterhead with the address of the private practice. There is some indication in the archives that an implicit agreement was reached between Naffziger and the dean’s office (the dean in 1947 was Francis Scott Smyth) that staff from the private practice would augment the duties required to perform university administration incumbent of a chair of department. Rules governing the relationship between faculty and private clinics were not yet fully developed, and this would lead to interesting discussions in years to come about the division of responsibilities and remuneration in clinical practice, some of which we will see in regard to the future administration of neurosurgery.

Naffziger’s appointment as Professor of Neurological Surgery and the creation of his own specialty department was not the only administrative change in 1947. When he ceased being chairman of the Department of Surgery, he was replaced in that position by H. Glenn Bell, Naffziger’s early recruit and co-designer of the surgical residency training program. Bell went on to a distinguished career pioneering the surgical treatment of breast, stomach, and colon cancer, and studying biliary tract disease.²⁰ He

remained Chair of Surgery until 1956 when Dr. Leon Goldman was appointed to the position.

Also in 1947 an external assessment organized by Dean Smyth on a proposal to establish neurology as its own department resulted, against the early objections of the Chair of Medicine William Kerr, in its creation that year. Robert Aird, who was director of the EEG laboratory, head of the epilepsy clinic, member of the school’s curriculum committee and strong advocate for reform in the instruction of neurology, as well as a researcher whose projects crossed several department and school lines, was appointed chairman of the new department.²¹

With a university slowly and laboriously, yet determinedly, committed to building a new campus with a focus on research, and with a departmental structure forming, the stage was set for rapid progress in neurological surgical teaching, research, and patient care as a new era began in the 1950s.



UC Neurological Surgery faculty and residents in the mid-1950s. Front row (left to right) John Adams, Howard Naffziger, Edwin Boldrey, Ottiwell Jones. Back row: Byron C. Pevehouse, Edward Keller, Gale Clark, J. Foster, Franklin Keville, Robert Dunbar, Robert Palmer, Irving Betts, Jose Aguilar, Daniel Meub, N. Jones. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.

Endnotes

- 1 Harvey Cushing, "The Special Field of Neurological Surgery after another Interval," *Archives of Neurology & Psychiatry* 4 (1920), 603-637, p. 603.
- 2 Naffziger and H. Glenn Bell, "The Post-Graduate Training of Students in Surgery at the University of California," *The Western J of Surgery, Obstetrics and Gynecology* (July, 1932), XX.
- 3 Cushing (1920) (op. cit.), p. 604.
- 4 Cushing (1920) (op. cit.), p. 607.
- 5 Christian Herter, "Imagination and Idealism in the Medical Sciences," *JAMA* 54: 6 (1910), 423-431; see analysis in Brian Dolan, *Humanitas: Readings in the Development of Medical Humanities* (San Francisco: University of California Medical Humanities Press, 2015).
- 6 W.C. Hanigan, "Surgery of the Head and 70-Day Brain Surgeons," *Neurosurgery* 53:3 (2003), 713-721, for the Army Neuro-Surgical Laboratory. K. Ro, J.L. Cameron, and

- M.W. Yeh, "The Hunterian Laboratory of Experimental Medicine," *Annals of Surgery* 253: 5 (2011), 1042-1048.
- 7 *Biennial report of the President of the University on behalf of the Regents* (1913), p. 136.
- 8 "Bonds for State Buildings and University Buildings," California Proposition 10 (1926), catalogued at UC Hastings School of Law Scholarship Repository: http://repository.uchastings.edu/ca_ballot_props/210.
- 9 Foster Kennedy, "Dr. Howard Naffziger," *Journal of Nervous and Mental Disease* 99:5 (1944), 461-462.
- 10 Nancy Rockafellar, ed., *Conversations with Dr. Robert B. Aird* (San Francisco: UCSF Oral History Program, 1995), p. 21.
- 11 Howard Naffziger, "The Surgical Treatment of Progressive Exophthalmus following Thyroidectomy," *JAMA* 99 (1932), 638.
- 12 R.B. Aird, "Experimental Exophthalmos and Associated Myopathy Induced by Thyrotropic Extract," *AMA Arch Ophth* 24 (1940), 1167-74.
- 13 Byron Pevehouse, "Edwin Barkley Boldrey, MD, 1906-1988" *Journal of Neurosurgery* 69 (1988), 813-814.
- 14 "Report of the Subcommittee on Recommendations Concerning the Operating Room Suite at the University of California Hospital" (Sept 16, 1948), from UCSF Archives and Special Collections, Boldrey Archive, MSS 84-22, papers 1946-1958, Folder "Committee on Operating Rooms."
- 15 Bertram Feinstein, W. Watson Alberts, Elwood W. Wright, and Grant Levin, "A Stereotaxic Technique in Man Allowing Multiple Spatial and Temporal Approaches to Intracranial Targets," *Journal of Neurosurgery* 17 (1960), 708-720; see also Benjamin Libet, *Mind Time: The Temporal Factor in Consciousness* (Cambridge: Harvard University Press, 2004), pp. 28-31.
- 16 John E. Adams, "The Development of Neurosurgery in Northern California," *Surg Neurol* 39 (1993), 90-93.
- 17 Adams (1993) (op. cit.), p. 93.
- 18 Naffziger Archive, UCSF Archives and Special Collections, MSS 97-004, Box 1, Folder 2, Autobiographical Notes, p. 18.
- 19 Bancroft Library, Berkeley, Office of the President Records, 1929-1958, CU-5, Series 3, Box-Folder 40:23 420 "Future of the Department of Neurology and Neurological Surgery - Committee Reports 1953-1954."
- 20 Albo (2005) (op. cit.).
- 21 Rockafellar, *Aird* (1995) (op. cit.), pp. 48-51. The external reviewer who recommended the creation of the Department of Neurology was Dr. Charles Aring, professor of neurology at the University of Cincinnati, who was recommended for the role by Glenn Bell.

Chapter Four

The Dawn of a Post-Naffziger Era in Neurological Surgery at UC



John E. Adams



Robert B. Aird



Lawrence H. Arnstein



Patricio Beltran



Edwin B. Boldrey



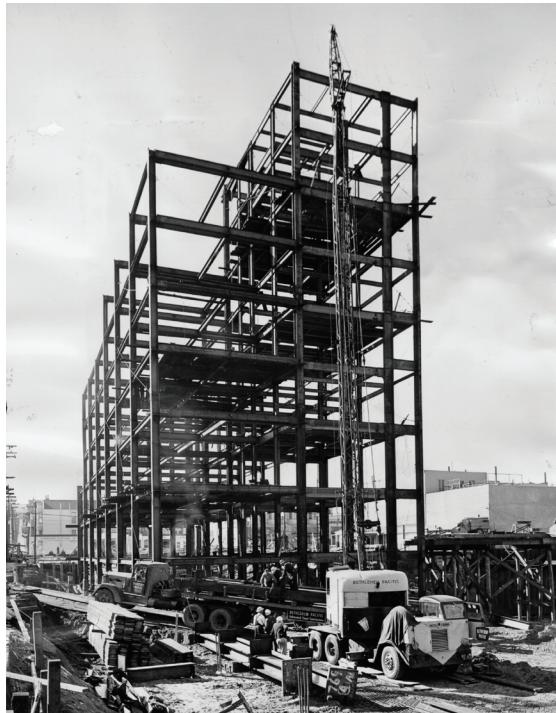
Howard A. Brown

“It is perhaps characteristic of Dr. Naffziger, that up until two weeks before his death he was still extremely active and busy in developing plans for the utilization of the funds which he had accumulated during his long professional career.”

– John Adams, MD

In 1951, Naffziger retired as chair of the Department of Neurological Surgery, but his work at the University was far from complete. One of his last acts as chair was to write to UC President Robert Gordon Sproul on the topic of the challenges of maintaining a private clinical practice for referrals and to provide the full scope of their practice while also treating “service” patients without fee at the University Hospital and training residents. The problem, as Naffziger saw it, was the separation of space and activities that took

Construction of six-story addition to Mount Zion Hospital. 1949.



place in the different “private” and “public” spheres. “Isolation of an able faculty of investigators is not in the interest of any concerned,” wrote Naffziger.

“Under ideal conditions a medical center to be great and to fulfill entirely its functions should afford its advantages to all of society and not only to the indigent. To accomplish this need a private hospital of sufficient size to permit not only the clinical staff to house their private patients but also to be a hospital open to the general profession is required. Such an institution could be expected to develop as a consulting center for the more serious medical problems.”¹

There is no extant reply from President Sproul but these recommendations were on the heel of plans already in development to expand the UC hospital network. In 1946 the Hill-Burton Act

provided federal funding to build hospitals across the United States, resulting in new opportunities for hospital development and for partnerships. Negotiations on an affiliation agreement with Franklin Hospital (now the Davies Campus of the California Pacific Medical Center) resulted in Ottiwell Jones and Howard Brown starting a neurosurgical service there and eventually extending the residency program to those wards. In 1955, the Herbert C. Moffitt Hospital opened on Parnassus, further allowing an expansion of neurosurgery. In 1958 it was clear that Stanford University was posed to move its clinical services from San Francisco to Palo Alto and this would also impact UC services, including increasing the demands on neurosurgery.

Since the 1920s UC and Stanford had shared various hospital



*Franklin Hospital
Administrator
George Monardo
helping to raze a
section of the old
hospital while several
nurses watch. 1965*

spaces and services (though maintaining their separate practices) including at Laguna Honda and San Francisco County Hospital. In 1946 they divided the staffing at Fort Miley Veteran's Hospital. Interestingly, in the early 1950s, Stanford, just like UC, was contemplating the dilemma of unifying the different campuses of their university, concerned about the distance between its clinical facilities and its main campus. Between 1958 and 1960, just as UC was committing itself to expanding in San Francisco, Stanford gradually withdrew all of its clinical staffing and teaching from there and relocated to Palo Alto.² The impact of this on neurosurgery was discussed in the department's first published annual report, pointing out in 1959 that their service and space at San Francisco County Hospital immediately doubled.

Edwin Boldrey was appointed chief of the neurosurgical service there, succeeded in 1960 by Byron Cone Pevehouse, who had finished residency under Boldrey in 1958 and had just returned from a National Science Foundation fellowship. The Stanford move also resulted in the necessity of overseeing neurosurgical service at the VA for the full year instead of six months, a service overseen by Joseph Witt and Burton Wise.

The demands of a sudden increase in clinical service put pressures on time and ability to teach, though neurosurgery nevertheless maintained an active role in medical education, teaching third and fourth year medical students, as well as expanding the residency training program.

In the mid-1930s the American Medical Association had stipulated a three-year residency training

The cross-shaped Moffitt Hospital and the adjoining medical sciences building. The two buildings were designed to function as an integrated unit, with direct access between the basic science research units and the teaching hospital. Image from UCSF Archives and Special Collections.



program for specialties but, according to Harold Rosegay, only one resident in neurosurgery at UC was the “beneficiary” of this schedule until 1944. In 1950 the standard neurosurgical program consisted of one clinical year at the UC Hospital, one clinical year at the Franklin Hospital, and a third year of lab work in either neuropathology, EEG, neurophysiology, neuroanatomy, or clinical research. In 1954 the residency program was

increased to four years. By the mid 1960s, the training was five years.

As hospital commitments increased, the amount of clinical cases also increased, but at a measured rate. Analyzing the numbers, Rosegay captures the average annual caseload between 1956 and 1962 in the amounts represented in the box on the next page.³

On top of this there were also separate diagnostic procedures, not accounted here but which totaled approximately 464.

Admissions 700 – 800 annually
 ~ 500 operations
 brain tumor (75-90 cases)
 herniated lumbar disc
 procedures (60 cases)
 anterior cervical disectomy
 and fusion (30 cases)
 carotid ligation (20 cases)
 carotid thrombectomy (20 cases)
 chemopallidotomy (16-30 cases)
 aneurysm procedures (15-25 cases)
 stereotactic procedures (15 cases)
 procedures under hypo-
 thermia (13-22 cases)
 spinal tumor procedures (11-23)
 hypophysectomy (2-15 cases)
 trigeminal root section (8 cases)
 angioma (4 cases)
 Selverstone clamp
 procedures (4 cases)

Changing Chairmanships: Growing Pains

In 1951 Dean Smyth recommended to President Sproul that Edwin Boldrey be promoted to full Professor of Neurological Surgery and appointed acting chair of the Department of Neurological Surgery.⁴ The next year the President confirmed Dean Smyth's appointment of Boldrey as chairman.⁵ Also in 1951, and with Naffziger's encouragement, John Adams was advanced to the top rank of the assistant professor scale, having only the year before been advanced from instructor. The next year, 1952, Adams requested an accelerated promotion to associate professor. After careful consideration, the review committee denied Adams' request, stating that an accelerated promotion was



Nurse Elaine Lindbeck standing in a corridor of the clinical study center at San Francisco General Hospital, 1964. Image courtesy of the San Francisco Public Library Historic Collection.

A nurse measures the pulse of one of the neurosurgical department's post-operation patients. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.

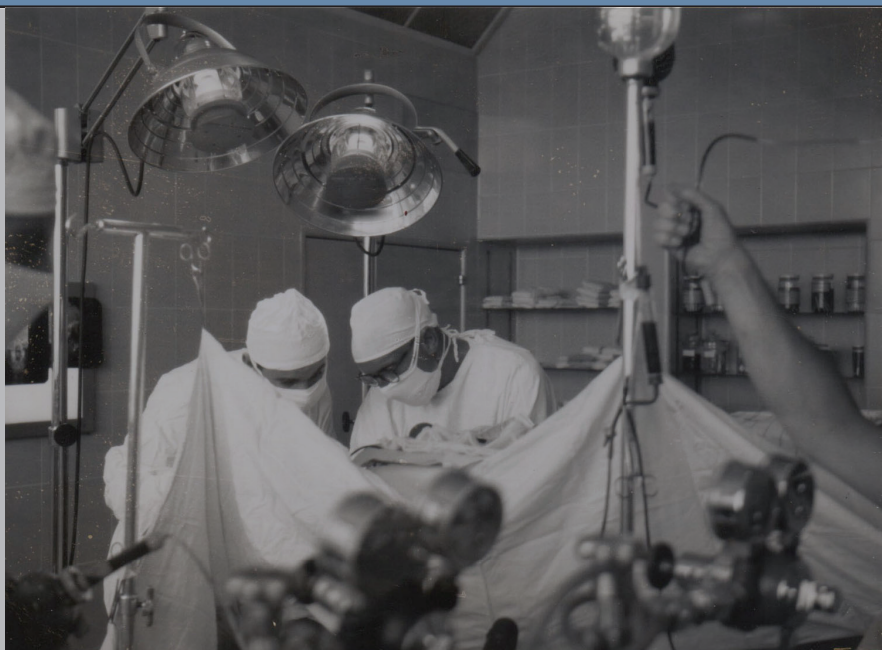


“unjustified at this time.” Behind the scenes, Boldrey had offered a discouraging critique of Adams’s departmental performance to the Dean and to Glenn Bell, Chair of the Department of Surgery (which suggests that, whatever autonomy the Department of Neurological Surgery had through its post-1947 organization, personnel matters may still have been routed through Surgery). In essence, Boldrey accused Adams of expanding his private practice so far around northern California that extensive travel resulted in too much time away from the medical school, neglecting ward walks, conferences, and other departmental functions.⁶

The matter was not quickly resolved. In 1953 the President appointed a committee to investigate “the status of Dr. John E. Adams,” and they determined that Boldrey’s leadership as chair – specifically in not approaching Adams first to discuss his

concerns – lacked judgment and adversely affected departmental morale. Boldrey said that he had been uncertain as to how to proceed since he feared that “any overt action against Dr Adams might bring him into conflict with his former chief,” who was, of course, Naffziger, a strong advocate for Adams’s promotions.

In an ironic conclusion, the committee took the opportunity further to criticize Boldrey’s own investment in the private neurosurgical practice he joined with Naffziger and others in downtown San Francisco, a practice which Adams himself had been a part until 1951. “This committee feels that such a professional relationship as Dr. Boldrey’s may lead to proprietary control of a department which will tend to confine opportunity, recognition, and advancement to members of the downtown office only, thus discouraging the utilization and development of any other talent. Furthermore



such an association tends to impair the freedom of action of the departmental chairman and to divide his interests and loyalties. This growth of this Medical School should long since have precluded such an alliance.”⁷ As we saw above, the issue of the relationship between private and university service was an issue that Naffziger himself had approached the UC President about and an issue that would clearly impact the way departments in the medical school were structured in the future.

The committee’s recommendation was first that Boldrey terminate his connection with the downtown office and that he consider more carefully “the spirit” of leadership laid down in the annual directive of the president to avoid internal conflict such as this. They also recommended that Adams be given specific clinical assignments “to display his ability, capacity, and state of development.” With that accomplished,

Adams was promoted to associate professor and appointed vice-chair of the department in 1954, working alongside Boldrey.

This story is recounted here not just as a vignette of leadership dynamics in the evolution of the department, but because this event was linked to a broader question the dean of the medical school raised about the status of neurological surgery altogether, which leads to an important moment in its history.

Recalling that the years between 1953 and 1955 were formative in plans to settle upon an appropriate organizational and departmental structure for the San Francisco campus, the dean asked the same committee that examined the question of Adams’s promotion to explore options with regard to the departments of neurosurgery and neurology. Specifically, Leon Goldman, a member of the Department of Surgery and future chair of surgery (1956-1963), was

Edwin Boldrey and Ottiwell Jones at a dinner function held for faculty of the Department of Neurological Surgery in August 1969.



asked to chair the committee to study the following questions:

- a) *Should they be continued as separate departments?*
- b) *Should they be returned to their respective parent departments, ie, Surgery and Medicine?*
- c) *Should they be combined in a department of Neurological Science?*
- d) *What faculty positions are basic to your recommendation?*

At the time (1953-1954), the total annual budget for neurological surgery was \$45,800. The department had three FTEs (Boldrey, Adams, and Robert Dunbar), one full-time secretary, two half-time secretaries, one full-time laboratory technician, and one half-time editor. The Department of Neurology, chaired by Robert Aird, had an annual budget of \$60,609. According to the committee, it had 4.9 FTEs and 3.2 secretarial FTEs, which was described as “a disproportionately large budget for such a specialty.”

The committee stated that “the strong mutual objection of each departmental head in accepting the other as chairman would create difficulties,” and while there was complementary teaching and research activities, it was recommended that the two departments “continue to exist autonomously at the present time.” However, with regard to the budget disparity, the committee also recommended increased support to appoint an assistant professor “to bolster the research arm of the [neurosurgery] department,” determining that neurology and neurosurgery would both have four faculty FTEs. This set an interesting, and perhaps unintended, precedent for distributing resources equitably between the two departments for the next decade, possibly impacting opportunities for individual growth.



John Adams and Robert Chow at a dinner function held for faculty of the Department of Neurological Surgery in August 1969.

Stereotactic Surgery Investigations

In 1954, John Adams traveled to Sweden to visit the neurosurgical clinic of Lars Leksell at the University of Lund. Leksell had recently published papers on the applications of a device used for what he termed stereotactic radiosurgery, where narrow beams of radiant energy, in the first instance x-rays but later gamma rays, were cross-fired at intracerebral nervous tissue. The device became known as the Leksell frame, which was a modification of earlier apparatuses that were fit onto the skull to provide a coordinate system using X (lateral), Y (anterior-posterior), and Z (inferior-superior) axes to localize desired targets for surgical interventions.

The conceptual developments of stereotactic surgery began with the collaboration between Robert Clarke, a British engineer and surgeon, and neurosurgeon Victor Horsley, who devised an

instrument for calculating two-plane Cartesian coordinates and used it on animal experiments in the first decade of the twentieth century. Ernest Spiegel and Henry Wycis at Temple University in Philadelphia first conducted stereotactic surgery on humans in the 1940s, which is when Leksell visited them. When he returned to Sweden, Leksell further refined the device by introducing three polar coordinates as well as the arc-centered concept, which allowed a probe to follow an arc giving it freedom of movement but remaining always pointed to the exact coordinates of the selected intracerebral target.⁸ Such an instrument was also timely in regard to advances in the production of brain atlases that identified localized structures based on detailed dissections, such as neurosurgeon Jean Talairach's coordinate system that could be used with landmarks defined from radiographic procedures.

Below: The stereotaxic apparatus, from "Investigation of the Central Nervous System, methods and instruments" by R.H. Clark (1920)

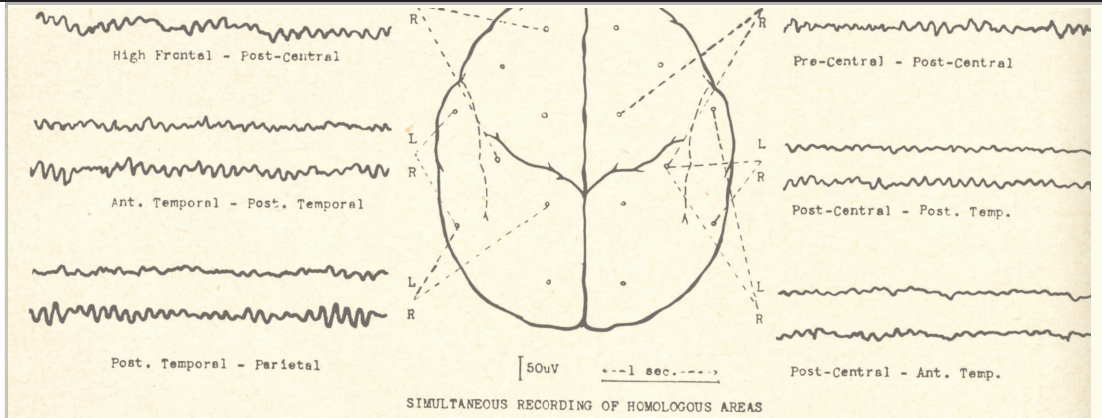
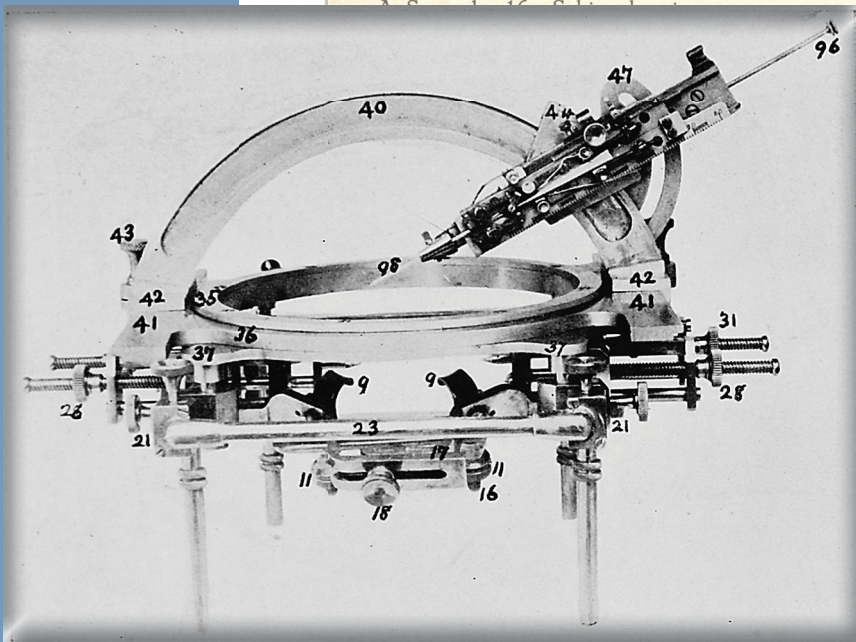


Fig. 3
SIMULTANEOUS RECORDING OF HOMOLOGOUS AREAS

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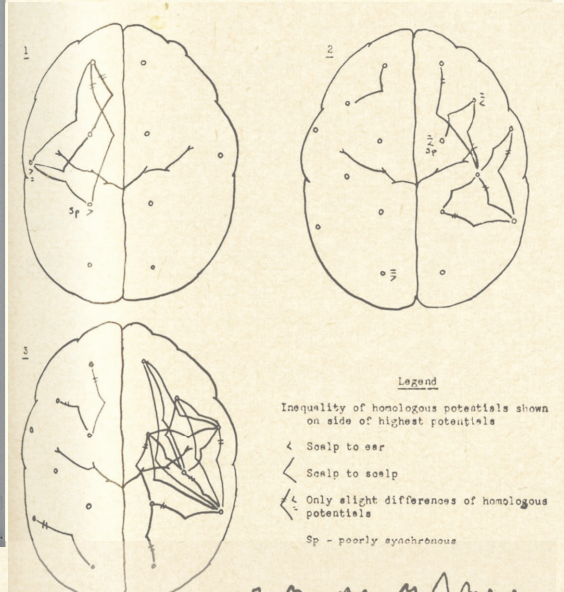


Fig. 4
SUCCESSIVE SPOT GRAPHS

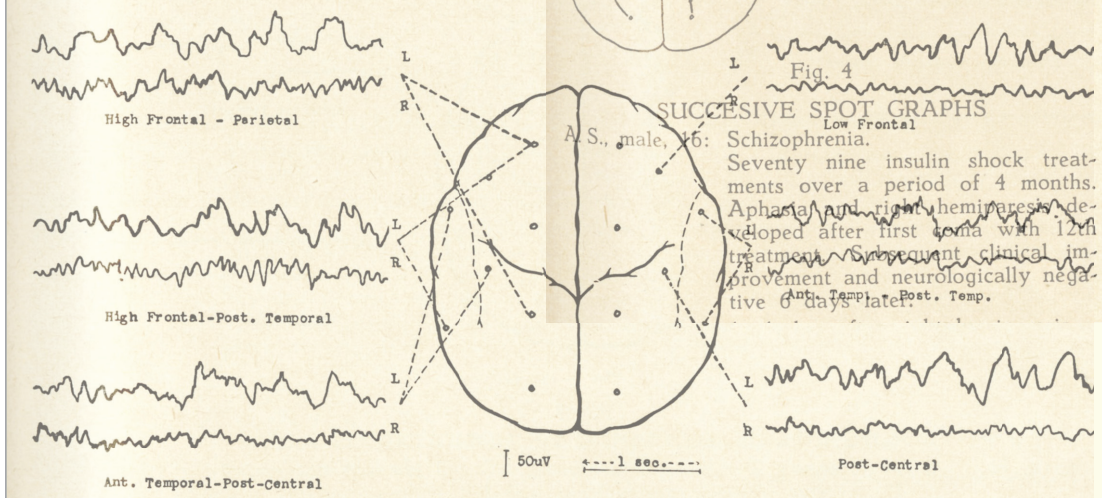
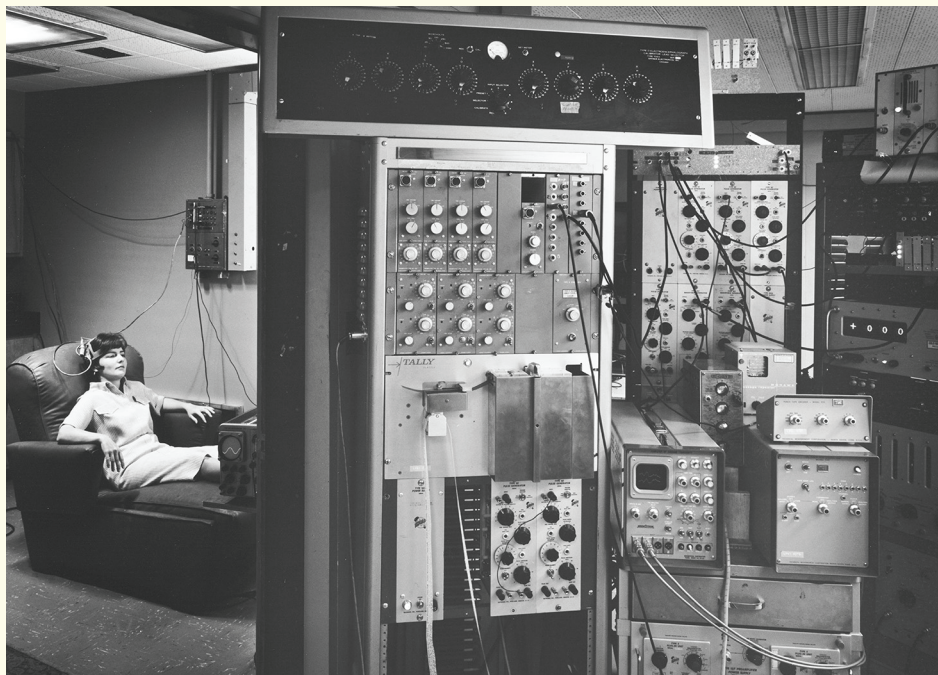


Fig. 6
SIMULTANEOUS RECORDING OF HOMOLOGOUS AREAS

A.O., male, 66: Head injury 2 months before entry. Dazed but not unconscious. Progressive aphasia, unsteadiness and left temporo-parietal headache.
 Examination: Mental slowing with mild aphasia, anomia and apraxia. Astereognosis of right h Staggering gait and tendency to fall to right. Associated movements poorly perfor on right.
 Lumbar Puncture: Initial pressure of 210 mm. H₂O. CSF normal.
 EEG: (Pre-operative) Gross focal dysrhythmia- left fronto-temporo-parietal.
 Operative Findings: Extensive subdural hematoma (200 cc. of old blood) in temporal, parietal posterior frontal regions on the left.

Images to the right: Successive spot graphs featured in "The localizing value and significance of minor differences of homologous tracings as shown by serial electroencephalographic studies" by Robert Aird, MD and John Adams, MD, *Electroencephalography and Clinical Neurophysiology*, 1952.



*Laboratory Research,
Langley Porter
Neuropsychiatric
Institute, San
Francisco Medical
Center, UC San
Francisco, August
1964. Photo by Ansel
Adams, reproduced
courtesy of the
UCSF Archives and
Special Collections*

The results were considered promising for enabling small areas of nervous tissue to be located and destroyed to produce physiological changes with minimal unwanted disturbance. Its early adaptations were in the treatment of certain psychiatric disorders and the relief of Parkinsonian tremor. It also had limited application in the relief of intractable pain and was used to target the hypothalamus for the control of aberrant behavior in epileptic and schizophrenic patients. In 1954, Adams, looking for new ways to treat epileptic patients and expand the practice at the

Langley Porter Neuropsychiatric Clinic, wanted first-hand experience with this technique.

The result upon Adams's return to San Francisco was the development of the program for stereotactic surgery. With the advent of psychopharmacological agents such as chlorpromazine, the neurosurgical activities at Langley Porter had become relatively quiescent. However the clinic there was admirably equipped, with a screened operating room adjacent to x-ray facilities. The plan was to use these facilities for all of the stereotactic (also spelled

stereotaxic) surgeries with the majority of patients being hospitalized in the neurosurgical ward in a new addition of the Langley Porter Clinic. Projected expenditure was \$5,000 to revise the x-ray facilities. The project was in collaboration with Alexander Simon, Chief of the Langley Porter Neuropsychiatric Institute, and Enoch Callaway, Director of Research there. With their help, equipment was available for electro-physiological stimulation and recording from both cortical and subcortical levels. The research facilities for studying patients pre- and post-operatively from the behavioral and psychological aspects were excellent, according to Adams. This program was promising not only because it provided a use for a facility that was at risk of being underused, but because the research opened the possibility of new treatments for patients presenting with new problems. Toward the end of the 1950s, clinical activity statistics at Moffitt Hospital showed a decrease in the number of brain tumors admitted, but a considerable increase in the number of complicated pain problems and such problems as recurrent and previously operated on intervertebral disc disease.⁹ The stereotactic surgery investigations therefore in part folded into an associated project

that had been of some time in the department: the treatment of pain.

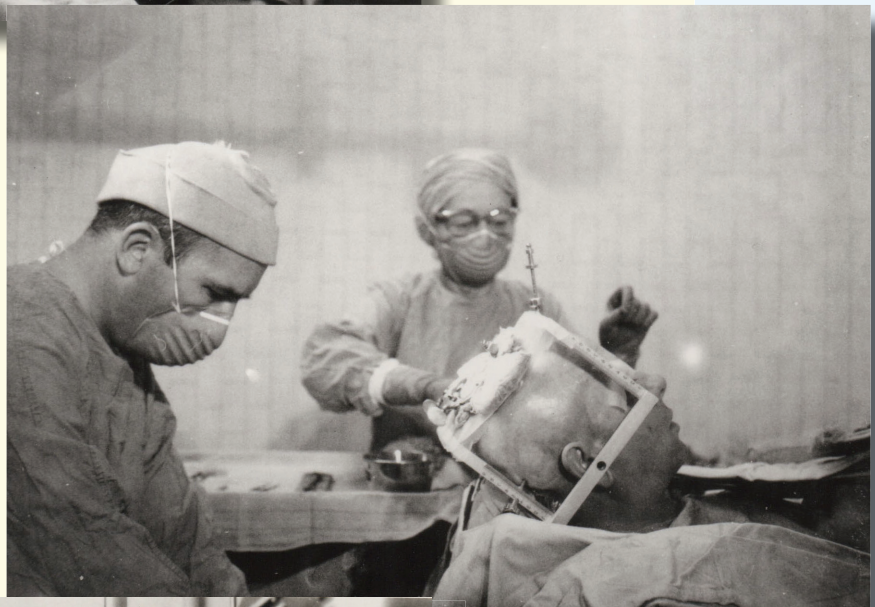
In 1956, Boldrey stepped down as chair of the department and Adams became chairman. In 1960, as the Stanford University Medical School move to Palo Alto was completing, Boldrey was appointed chief of the neurosurgical service at San Francisco General Hospital. Even as chair, Adams continued to develop research and experimental trials in the department, including continuing his own investigations in stereotactic surgery.

In 1958, Adams recruited Joseph Witt to supervise a stereo-encephalotomy program. Witt had received his medical degree from the University of Colorado and did his residency in neurosurgery at the Mayo Clinic. At UC, he helped to establish an out-patient clinic to evaluate pre- and post-operative patients referred for this type of surgery, namely patients with Parkinson's disease, cerebral palsy, epilepsy, and intractable pain problems.

By 1961, the operating room at the Langley Porter Institute was used exclusively for stereo-encephalotomy procedures, and handled two to three cases per week. At this time Adams reported several problems that were being studied:



UCSF neurosurgeons by the mid-twentieth century depended upon a mixture of traditional surgical equipment and more modern surgical devices with technology that reflected broader advances of the time period.



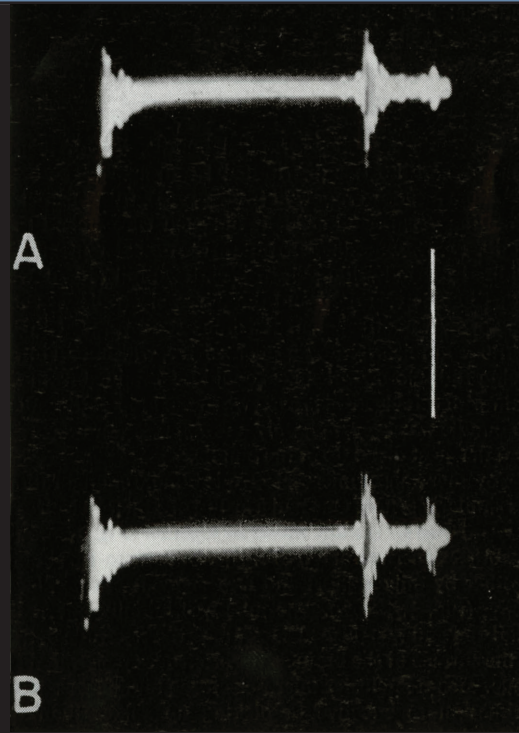
Operating rooms hosting an intracranial procedure potentially featured, for example, the stereotactic frame as well as motion picture cameras.

Image featured in "Indwelling multiple micro-electrodes in the brain" by Elwin Marg, MD and John Adams, MD, *Electroencephalography and Clinical Neurophysiology*, 1967. This image is an x-ray of implanted micro-drive with the free-cluster micro-electrode bundle. Fine curved wires seen around it are metal sutures.



- (A) Comparison of methods of lesion production
 - a. Radio frequency thermocoagulation
 - b. Temporarily applied intense beta-emitting isotopes carried in a stereotactic probe
 - c. Comparison of these to those produced by the proton beam and cryogenic techniques to follow the present series.
- (B) Evaluation of currently utilized target localization procedures compared with newer techniques requiring much less time and instrumentation
- (C) Establishment of a standardized set of parameters of stimulation and means of recording responses to allow comparison of apparently divergent responses reported from different study groups throughout the world.

In a relatively short period of time, the growth of interest in stereotactic surgery internationally was beginning to make it look like a new sub-specialty of neurosurgery, while paradoxically forging new connections between neurosurgery and other disciplines, breaking down previous conceptions of specialized practices. The tremendous growth of medical knowledge and expanding complexity of medical technology led to interesting concerns for the department in the early 1960s. In the wider context, stereotactic surgery was now organized as a professional society and had a new journal devoted to this branch of neurosurgery. While this is conventionally a hallmark of specialization, the discipline also generated increasing connections between previously well compartmentalized fields in the



Ultrasonic echo of an animal's brain with free-cluster micro-electrode bundle inserted. Signal at the left is the transducer; signal at the right is the dura mater. The vertical line points to the echo of the electrode bundle above (A) and to the larger signal caused by an electrolytic bubble at one micro-tip below (B). This demonstrates how in principle a small electric current can be used for tip localization.

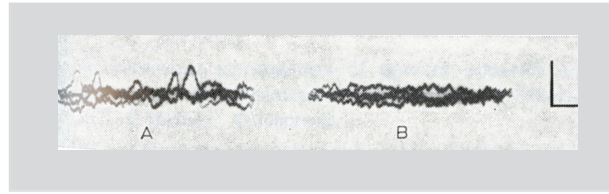
biological and physical sciences. "Neurological surgery," wrote Adams, "as a branch of medical science and practice at this institution, is beginning to feel these pressures and forces. The obvious reliance and dependence of stereotactic techniques upon electronics, physics, etc., illustrates the point."

Such were the concerns of the chair of the department who happened also to be the one who spearheaded this developing area of neurosurgery. This example also indicates more general considerations that were being given to the future of neurosurgery as a result of its increasing attention to areas, both clinical and research, that generated further degrees of specialized knowledge. "It is frequently suggested that with the dilution of neurological surgery occurring in this country, each center should have an 'aneurysm surgeon' so that this difficult

surgical problem can be delegated to a single individual who would thus become more proficient in the management of such patients," wrote Adams. However advantageous such a plan might seem, the question that emerged from the experience of the past few decades regarding the organization and training of individuals was how to maintain balance and perspective with increasing fragmentation of an already restricted field. "I am sure similar questions are being asked at all neurosurgical centers," he concluded, reflecting interesting dilemmas facing the growing field of academic neurological surgery.¹⁰

The stereotactic surgical ward at Langley Porter continued to become more refined as the practice developed, with innovations in technique and patient care. To illustrate the practice, the clinical team, lead by Witt, commented that they had difficulty

“Single unit potential in the striate cortex which showed activity when the eyes were open (A) but inhibition when the eyes were closed (B). Changes of luminance did not affect this response.”



demonstrating all the cardinal internal landmarks simultaneously on a single film and also in managing syncopal episodes in older patients using standard methods. These difficulties coupled with the need to maintain the patient's comfort during long periods of neurophysiological study led to the development of a new stereotaxic surgical bed. "A standard circ-electric bed was modified to hold the Leksell stereotaxic frame and x-ray cassettes to any desired position. With this motor-driven bed, the patient's position can be quickly altered and the positioning of the contrast material is accomplished with much greater facility." With the ability to change the patient's horizontal position quickly, they developed an air injection technique that continuously demonstrated all the midline structures completely on a single film. They also added considerably to the instrumentation, so that more than one electrode could be inserted simultaneously but with independent stimulating circuits to produce different parameters to evaluate the effectiveness of simultaneous small lesions as

opposed to one large lesion.

Experimentally, the department was collaborating with the Donnor and Livermore Radiation Laboratories to utilize an extremely intense stereotactically placed radioactive isotope in the therapy of deep-seated tumors in animals, and in conjunction with the department of neurology they were testing the therapeutic uses of implanted electrodes in intractable epilepsy as well as the use of computer techniques to analyze recordings obtained from peripheral, cortical, and subcortical leads.

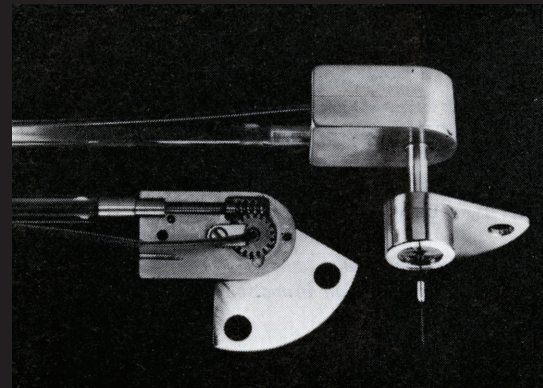
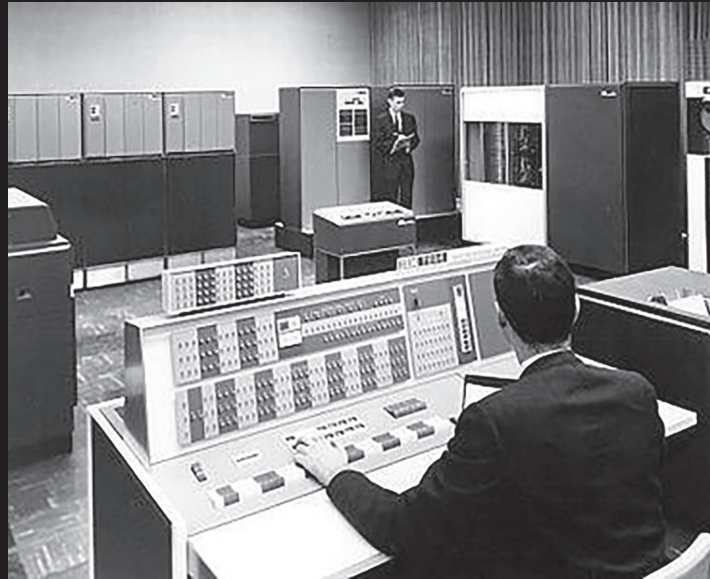
To cap a decade of clinical and research work in stereotactic surgery, Adams launched a study with a grant from the Vocational Rehabilitation Administration to investigate intractable and incapacitating epilepsy. Fine, multi-lead electrodes were stereotactically implanted in patients with severe, uncontrollable, temporal lobe seizures. This project was also interdisciplinary, with patients evaluated by a neurosurgeon, neurologist, psychiatrist, psychologist, someone from the social service department, as well as a vocational rehabilitation counselor.

In 1965, seven patients had been studied in the following manner:

“Bipolar electrode pairs 1 mm. apart have been placed in the hippocampal gyrus, the anterior hippocampus, the amygdala, the caudate nucleus, the non-specific and specific thalamic nuclei, including centrum medianum, and finally the posterior hippocampus. Daily recordings are obtained from these subcortical electrodes. Seizure activation is carried out by the intravenous injection of Metrazol and Lidocaine. The latter study has been done in conjunction with Doctor Rudolph De Jong in the Department of Anesthesiology. Seizure activation is likewise carried out by means of stimulation at the various electrode sites. The behavioral changes in relation to stimulation is likewise being studied in conjunction with the alteration in the subcortical and surface potentials.”

The physiological data were stored on a magnetic tape and processed with an analogue computer, but the department was in the process of moving digital with the use of an IBM 7094 computer in Berkeley – a new machine designed for “large-scale computer processing.” With this they aimed to draw “equi-potential lines” or maps throughout the brain by power-spectrum analysis and obtain a readout from the computer as to actual stereotactic coordinates of high potential sources. Their results and publications substantiated the work of others in finding that only with subcortical electrodes could one clearly delineate foci of epileptic nature in the temporal lobe. “The value of such studies,” wrote Adams, “from a behavioral standpoint is becoming more and more apparent, and Doctor Mardi Horowitz of the Department of Psychiatry is collaborating in this aspect of the work.”

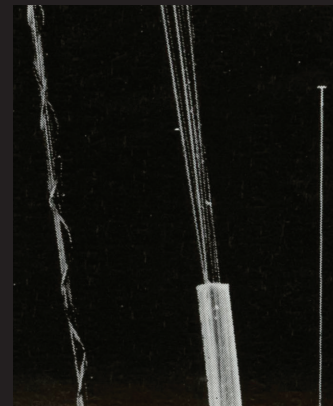
“Built for large-scale scientific computing, the IBM 7094 Data Processing System featured outstanding price/performance and expanded computing power.” IBM online archives. The 7094 was introduced in 1962 and sold until 1969.



Images middle and bottom: Implantable micro-drive with a free-cluster micro-electrode bundle. The cylinder above the bundle fits in the burr hole with the flange screwed to the skull surface.

Left is a wrapped cluster and next to it free-cluster micro-electrode bundle. The scale line to the right is 1 cm.

Thus were the origins of the operative techniques and procedures that would continue to develop at UCSF, which in 1991 evolved into the Gamma Knife and CyberKnife Radiosurgery program that we see today. While 1965 saw the results of a number of interesting studies in stereotactic surgery through publications, lectures, and even a closed-circuit TV program for the American Medical Association, it was also the year that Joseph Witt, the first research director of the program, passed away from a long and trying illness.



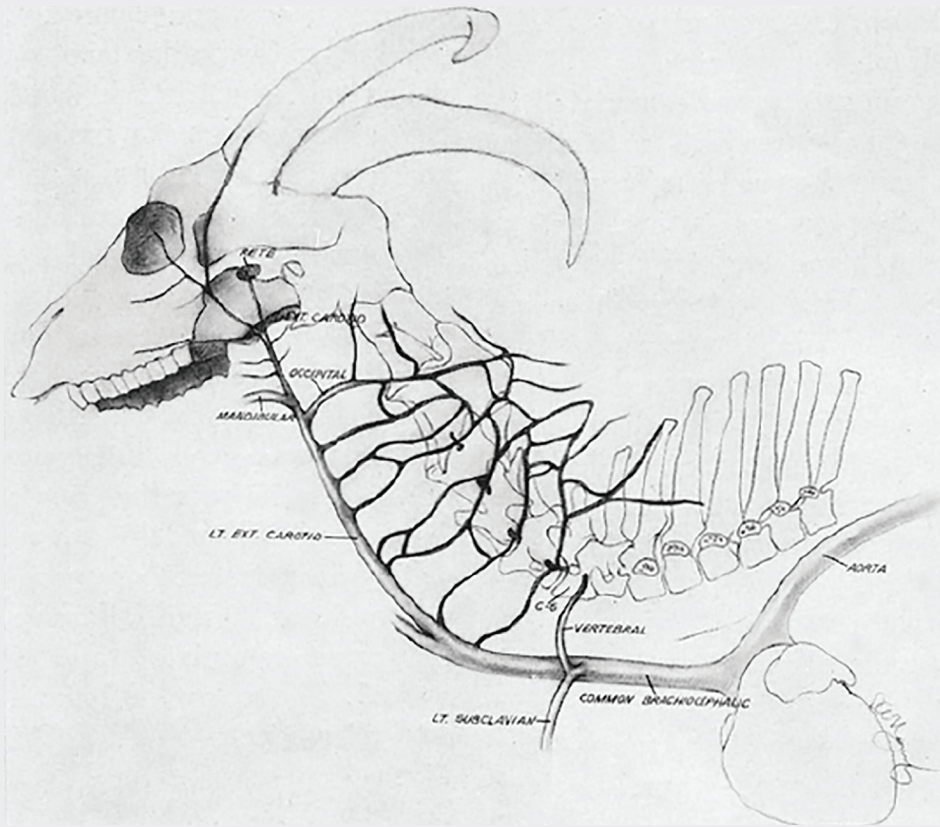


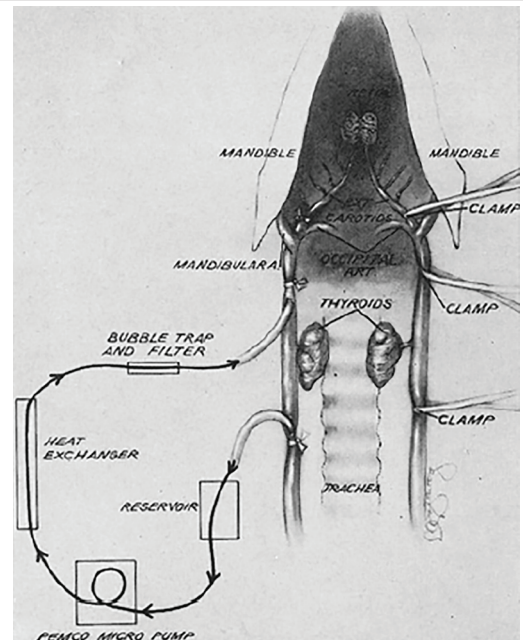
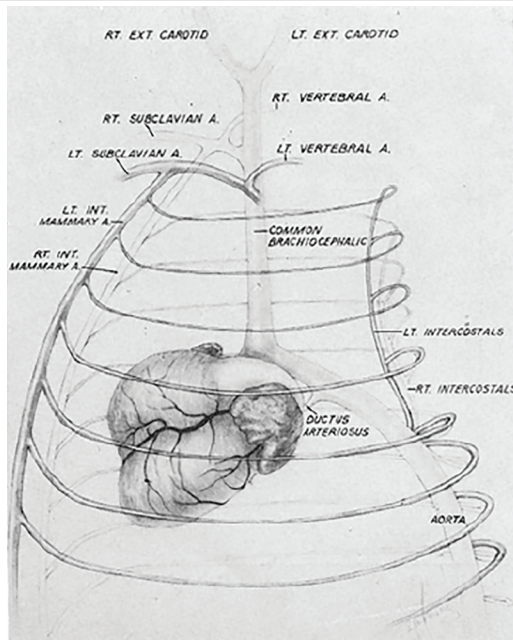
Illustration featured in "Occlusion of the blood supply to the brain of the goat: Protective effect of deep hypothermia" by Maurice C. Smith and John E. Adams, Journal of Neurosurgery, 1963. "Vertebral plexus of the goat. Note major vertebral-occipital arterial anastomosis as well as numerous carotid contributions to vertebral plexus."

Collaborative Investigations in Hypothermia

Another area of research that was developed in the 1950s and 1960s was the effect of low temperatures upon cerebral physiology. The initial aim was to explain the loss of peripheral vascular control when the temperature of the brain is reduced to approximately 20 degrees Celsius. The research was originally spearheaded by neurosurgical resident Byron Cone Pevehouse. Upon graduating in 1958, he received

a National Science Foundation fellowship to study at the Montreal Neurological Institute and the National Hospital in Queen Square, London. At that time, this research was continued by the new arrival to the department, Joseph Witt, who was able to oversee investigations in this area in the newly established Cerebrovascular Research Institute (1959).

Left: Anastomosis between aorta and common brachiocephalic system via the intercostal arteries. Right: Location of catheters and schematic diagram of extracorporeal system employed in regional hypothermia.

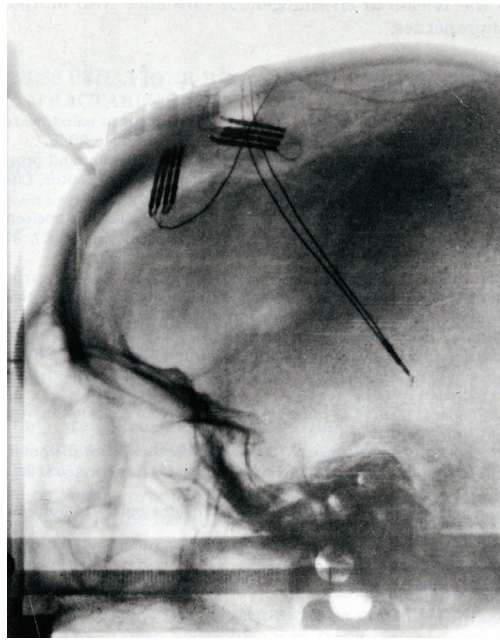
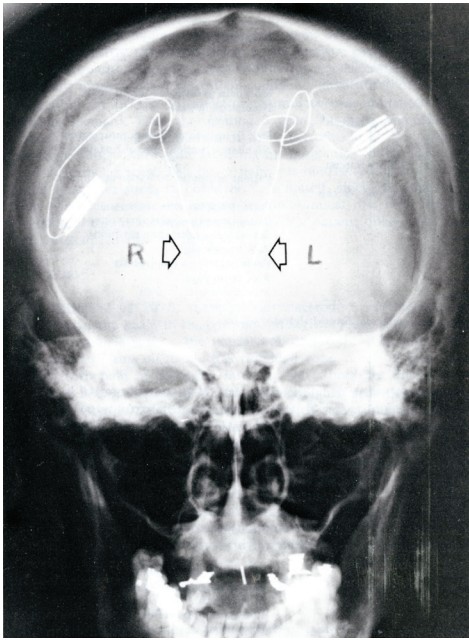


The project developed with the aid of data the research team obtained from cerebral arteriovenous samples prior to and immediately following the interruption of blood supply to the brain in patients undergoing operative procedures for intracranial vascular anomalies. The data led to the hypothesis that under conditions of hypothermia and occlusion of the blood supply to the brain there may be utilization of endogenous substrates within the brain rather than the exclusive reliance by the brain upon exogenous glucose as a source of energy. It was an idea that John Adams presented as a paper to the Harvey Cushing Society in 1960.

In the laboratory using goats, a DeBakey pump and a flowmeter, neurosurgery resident Norman Chater improved the technique of extracorporeal carotid artery-to-carotid artery differential brain cooling to control parameters such as perfusion pressure and

perfusion rate. He established that the sudden profound hypotension usually occurring when the temperature of the brain reached 24 degrees Celsius is a result of peripheral vasodilatation and a decreased cardiac output as a result of inhibition of central vasomotor tone. Approaching the problem another way, he developed a technique for locally perfusing the fourth ventricle and thereby the medullary centers with cold mock cerebrospinal fluid. When the medullary centers reached the temperature of 24 – 20 degrees Celsius, the same profound hypotension developed.

Over the next two years the hypothermia studies were continued by senior residents Maurice Smith and Paul Karlsberg, who developed a reproducible laboratory experiment with the concept that one hemisphere of the goat brain would be a control at normal temperatures, following which the temperature of the other



X-rays depicting position of electrodes. Images featured in "Naloxone reversal of analgesia produced by brain stimulation in the human" by John Adams, MD, Pain, 1976.

hemisphere will be lowered by an extra-corporeal cooling shunt. Their findings altered previously held beliefs that low temperatures do not constrict cerebral vessels but rather relax them, with the rise of perfusion pressure owing to the increased viscosity of cold blood into cerebral circulation.

Maurice Smith finished his residency and joined the clinical faculty in 1962, receiving a Giannini Fellowship that year to continue studies on cerebral vascular physiology and aspects of hypothermia, and became director of the Cerebrovascular Research Laboratory in 1964. The research moved from goats to primates that were cooled by various external means and rewarmed with diathermy. By combining hemodilution, slow cooling with ice, and careful control of the acid base balance, the animals were cooled to 20 degrees Celsius and rewarmed for an experiment to study the effects of Pronethalol in

preventing cardiac arrhythmias. Research was again interdisciplinary, carried out with the Department of Anesthesiology. The findings: "These studies demonstrated that with the proper preliminary dosage of Pronethalol, cardiac arrhythmias such as shifting pacemaker, ectopic foci, etc., could be abolished, but that Pronethalol would not prevent fibrillation when it was directly the result of cold injury to the myocardium. Nevertheless, it was shown that monkeys could be cooled successfully to 20 degrees C. and rewarmed and resuscitated without extracorporeal circulation." Although Pronethalol – which was an early non-selective beta blocker – was never clinically used, the results of these experiments resulted in clinical applications since it forewarned that cardiopulmonary bypass should be prepared for patients undergoing profound hyperthermia at specific temperatures for certain operations.¹¹

Howard Naffziger (left of center) walking with a procession of graduates and other faculty on the UCSF Parnassus campus in the early 1960s. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.



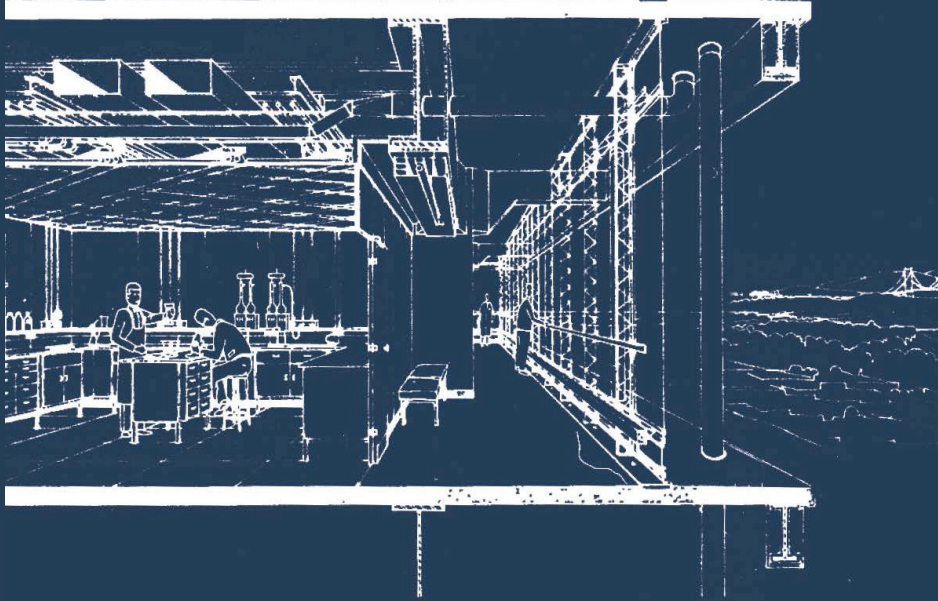
Laboratory Space

John Adams was chair of neurological surgery from 1956 until 1968. Embracing the Naffziger spirit of building neurosurgery through sound experimental research, he was extremely active in securing new space and promoting projects that would translate into clinical outcomes. He entered the chairmanship with a strong ally in Naffziger.

After his retirement in 1951, Governor Earl Warren appointed Naffziger a member of the Regents of the University of California. At a charter day celebration of the university in 1959, Naffziger presented an address to the UC President, his fellow Regents, and the audience, reflecting on the future of the UC Medical School and the Medical Center. "What then," he asked, "are the urgent needs of the Center? Undergraduate and graduate instruction are excellent, but the

physical facilities affording opportunities for investigative work and research are meager. At times they are stifling. Imagination and effort have been frustrated. This sounds very gloomy. However, bright spots have appeared. The transfer of experimental biology and medicine from Berkeley to the Hooper Foundation is one. The establishment of the Cancer Institute and the more recent development and opening of the Cardio-Vascular Research Center augur well for the future."¹²

His speech was well timed. It was in the midst of university plans to expand the San Francisco campus and consolidate departments there, re-establishing the basic sciences with the health sciences campus. Stanford was on its way to Palo Alto, leaving space open for clinical expansion. It was also on the cusp of the San Francisco campus gaining more autonomy in its affairs, with



*Architectural blueprint depicting laboratory space in the Health Sciences West research tower. Image adapted from Henry Bourne, *Paths to Discovery* (2011).*

the important moment of the first commencement ceremony separate from Berkeley happening in June 1961, with the head of the US Department of Health, Education, and Welfare Abraham Ribicoff as the principal speaker.

Laboratory space a topic near and dear to Naffziger, who first presented a proposal to his chair of department to establish a neurological surgery institute in 1926, and was still waiting to see that happen. It was something he would not see. In 1961 Naffziger died. "It is perhaps characteristic of Dr. Naffziger," wrote John Adams in a departmental notice, "that up until two weeks before his death he was still extremely active and busy in developing plans for the utilization of the funds which he had accumulated during his long professional career."

In 1960, neurosurgery had a close relationship with the Department of Neurology, chaired by Robert

Aird, sharing space as well as some administration and collaborative teaching. That year they shared just over 2,000 square feet of lab space in various buildings:

Neurophysiology Lab (room 430)	182 sq. ft.
Neurophysiology Lab (room 302, Old Medical School Building)	180 sq.ft.
Cerebral Blood Flow and Electrolyte Determination Lab	240 sq. ft.
Chemistry Lab	170 sq.ft.
Neurochemistry Lab	170 sq. ft.
Blood Brain Barrier Lab	270 sq. ft.
Animal Neurophysiology Lab	720 sq. ft.
Research Secretary's Office	150 sq. ft.

However, the new health science towers (then called the “Health Instruction and Research Building” but now known as Health Science East and West), were being constructed and plans were that neurology as well as neurosurgery would together be allocated 3,800 sq. ft. of new lab space. With plan for the recruitment of new faculty in neurosurgery, this was none-too-soon.

In 1963, the Regents approved the establishment of the “Howard C. Naffziger Institute for Neurological Research.” The plan was that initially the Institute would be housed in the research space allotted jointly to the Department of Neurology and the Division of Neurological Surgery in the new health sciences building, and that the Director would occupy the Guggenhime Chair of Experimental Neurological Surgery.

In 1966, neurological surgery did in fact move into the new space on the seventh floor of Health Sciences West but it was a tighter fit than anticipated, with the loss of a seminar room and four hospital beds to accommodate the expansion of the intensive care unit. It was also once again a trying period in terms of the administrative structure of neurological surgery.

In 1965, the chair of neurology, Robert Aird, was expressing his intention of stepping down as chair to focus more on research. With the medical school’s increased autonomy came, as he said, “endless administrative and

political nonsense, which by 1963 or 1964 had reached gargantuan proportions.”¹³ Pressure from the dean of the school of medicine, William Reinhardt, to remain in place until a replacement was found kept Aird in place until 1966. But during the year between 1965 and 1966, Reinhardt – known as a proponent of recruiting outside talent to lead departments – formed a committee to rekindle a decade’s-old consideration about formally uniting neurology and neurological surgery to form one department. With an endowment for a professorship from Berthold and Belle N. Guggenhime to use, in 1966 the dean brought out a neurosurgeon from the East Coast with an offer of a chairmanship, which was conditional on the combination of the departments. The proposal led to “unrest” in neurosurgery and – since this candidate was rumored to be antagonistic toward the growth of neurology at his own campus – was rejected by Aird. In the end, the dean appointed Robert Fishman, a physician from the Neurological Institute at Columbia Presbyterian Medical Center, to chair the Department of Neurology.

In 1968, John Adams retired as chair of neurological surgery and was appointed the first Guggenhime Professor of Neurosurgery. That year, he took a sabbatical and returned to Europe to visit centers of stereotactic surgery—a program that he promoted so thoroughly at UCSF. As the 1960s drew to a



UC Neurosurgery Faculty and Residents around the mid-1950s. Front row (left to right) John Adams, Howard Naffziger, Edwin Boldrey, Ottiwell Jones. Back row: Byron C. Pevehouse, Edward Keller, Gale Clark, J. Foster, Franklin Keville, Robert Dunbar, Robert Palmer, Irving Betts, Jose Aguilar, Daniel Meub, N. Jones. Courtesy of Archives and Special Collections, Library and Center for Knowledge Management, University of California, San Francisco.

close, Adams's chairmanship was reflected on as over a decade's achievements in expanding neurosurgical research, laboratory space, cross-departmental collaborations, and faculty recruitment. The amount of research grants brought in also increased: in 1958, the department obtained \$79,000 in external funding; in 1960, it had risen to \$99,000. By the end of the 1960s, hundreds of thousands of dollars, with individual grants totaling above \$100,000, were obtained for neurological surgery

research, primarily at this time in the area of brain tumor research.

This development was intimately bound to the appointment in 1968 of a new chair of neurological surgery, Charles B. Wilson, who was recruited from the University of Kentucky where he was making a name for himself as a pioneer surgeon of pituitary tumors. His arrival in San Francisco marked the beginnings of major new developments for the division of neurosurgery at UCSF.

Endnotes

- 1 UCSF Archives and Special Collections, Naffziger Archive, Box 3, Folder 102, "UCSF Correspondence."
- 2 See the brief account by Joseph LaDou, "UCSF Stanford Merger," http://history.library.ucsf.edu/stanford_merger.html.
- 3 Rosegay (1996) (op. cit.), p. 798.
- 4 Bancroft Library, UC Berkeley: Office of the President Records, 1929-1958, CU-5, Series 3, Box 15: Folder 32, "Promotion of Edwin B. Boldrey."
- 5 UCSF Archives and Special Collections, Boldrey Archive MSS 84-22, Papers 1946-1958, "Appointments."
- 6 Bancroft Library, UC Berkeley: Office of the President Records, 1929-1958; CU-5 Series 3, Box-Folder 40:23 420 Future of the Department of Neurology and Neurological Surgery - Committee Reports 1953-1954; also CU-5, Series 3, Box 15: Folder 31, "Status of Dr John E Adams."
- 7 Bancroft Library, UC Berkeley: Office of the President Records, 1929-1958, CU-5, Series 3, Box-Folder 40:23, f. 420 Future of the Department of Neurology and Neurological Surgery - Committee Reports 1953-1954.
- 8 L. Leksell, "The stereotactic method and radiosurgery of the brain," *Acta Chir Scandinavia* 102 (1951), 316-319. T. Reichert and F. Munding, "Description and use of an aiming device for stereotactic brain surgery," *Acta Neurochir* 3 (Suppl) (1955), S3078-337.
- 9 "First Annual Report, Division of Neurological Surgery, University of California School of Medicine," 1958, p. 6.
- 10 "Fourth Annual Report: Division of Neurological Surgery 1961-1962," University of California School of Medicine, p. 1.
- 11 John Adams, "Clinical Experiences with Hypothermia," Chapter 12, in William Fields and Adolph Sahs, eds., *Intracranial Aneurysms and Subarachnoid Hemorrhage* (Springfield, IL: Charles C. Thomas Co., 1965).
- 12 Naffziger Archive, MSS 97-004, Box 1, Folder 1, speech written March 18, 1959, delivered March 28, 1959.
- 13 Aird in Rockafellar (1995) (op. cit.), p. 90.



John E. Adams



Robert B. Aird



Lawrence H. Arnstein



Patricio Beltman



Edwin B. Boldrey



Howard A. Brown



Glenn O. Cross



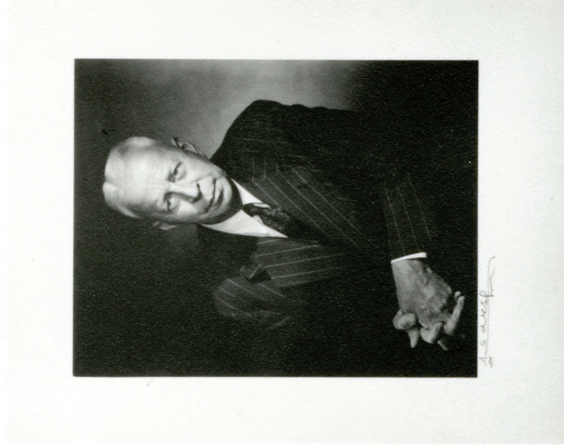
Edward W. Davis



Robert D. Dunbar



Howard W. Fleming



Harold C. Hoffpeter



Everett Hurteau



James Jenkins



Ottwell W. Jones, Jr.



William T. Grant



David O. Harrington



Thomas G. Huff



Lester B. Lawrence



C. E. Locke, Jr.



James C. Luce



Lyman Maase



Robert C. Martin



Edmund J. Morrissett



Nathan C. Novacek



John W. Pace



H. Jack Siefert



Frank P. Smith



W. Eugene Stern



Phillip Van Horn



Whin Kwei Wang



Eugene M. Webb



David S. Zealear

University of California Medical School

Neurological Surgery 1920-1951

RESIDENTS

Below: Group photo taken in the mid-1960s. Front row (left to right) Jacob Mathis, William Lee, George Martin, Jay Levy, Timothy Altenhofen. Back row: Louis Nelson, Bob Chow, John Adams, Ed Connolly, Earl Olsen.







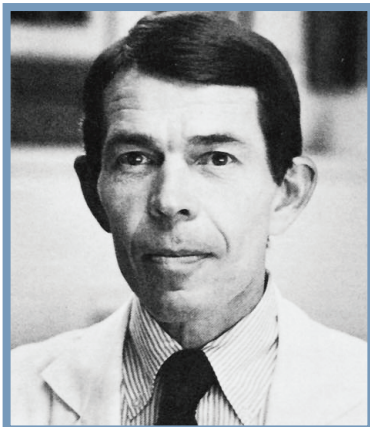




Chapter Five

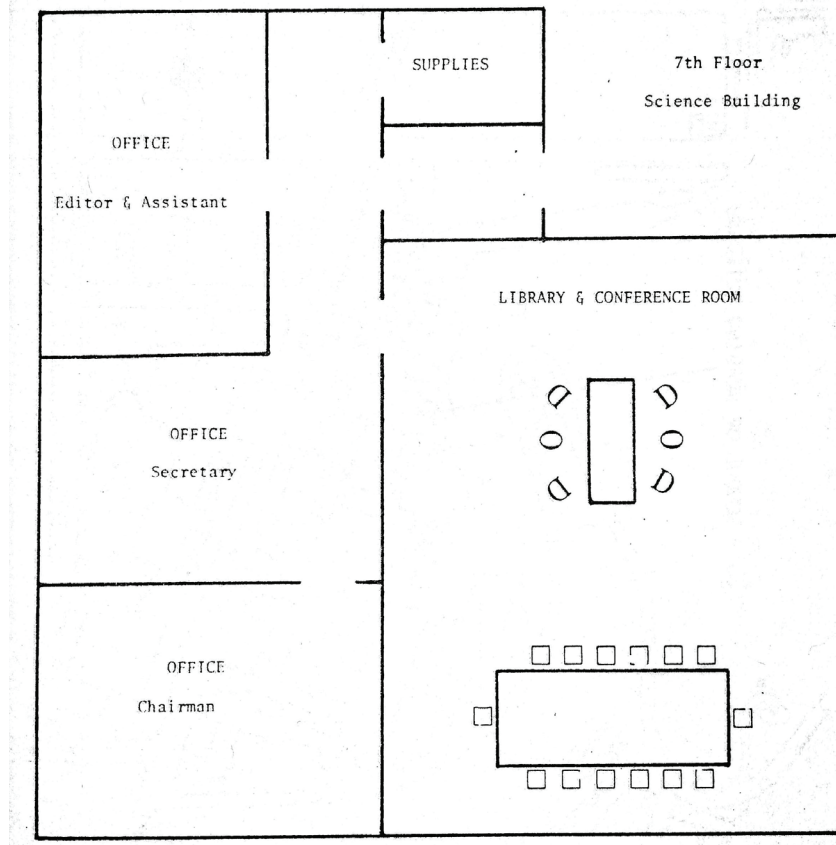
The Brain Tumor Research Center

This is indeed a very special day for me, for Neurological Surgery, and for the University of California. The dreams of four men become reality with today's dedication of the Howard C. Naffziger Laboratories for Neurosurgical Research. I believe that the first of these men would be pleased by the caliber of the laboratories that now bear his name.☺



DR. CHARLES B. WILSON
PROFESSOR AND CHAIRMAN OF THE DEPARTMENT
OF NEUROLOGICAL SURGERY
CORDIALLY INVITES YOU
TO ATTEND THE DEDICATION OF THE
HOWARD C. NAFFZIGER LABORATORIES
FOR NEUROSURGICAL RESEARCH
3 P.M., MAY 6, 1970
ROOM 1671
HEALTH SCIENCES INSTRUCTION AND RESEARCH TOWER
TOUR OF LABORATORIES AND RECEPTION FOLLOWING
ROOM 758
MEDICAL SCIENCES BUILDING

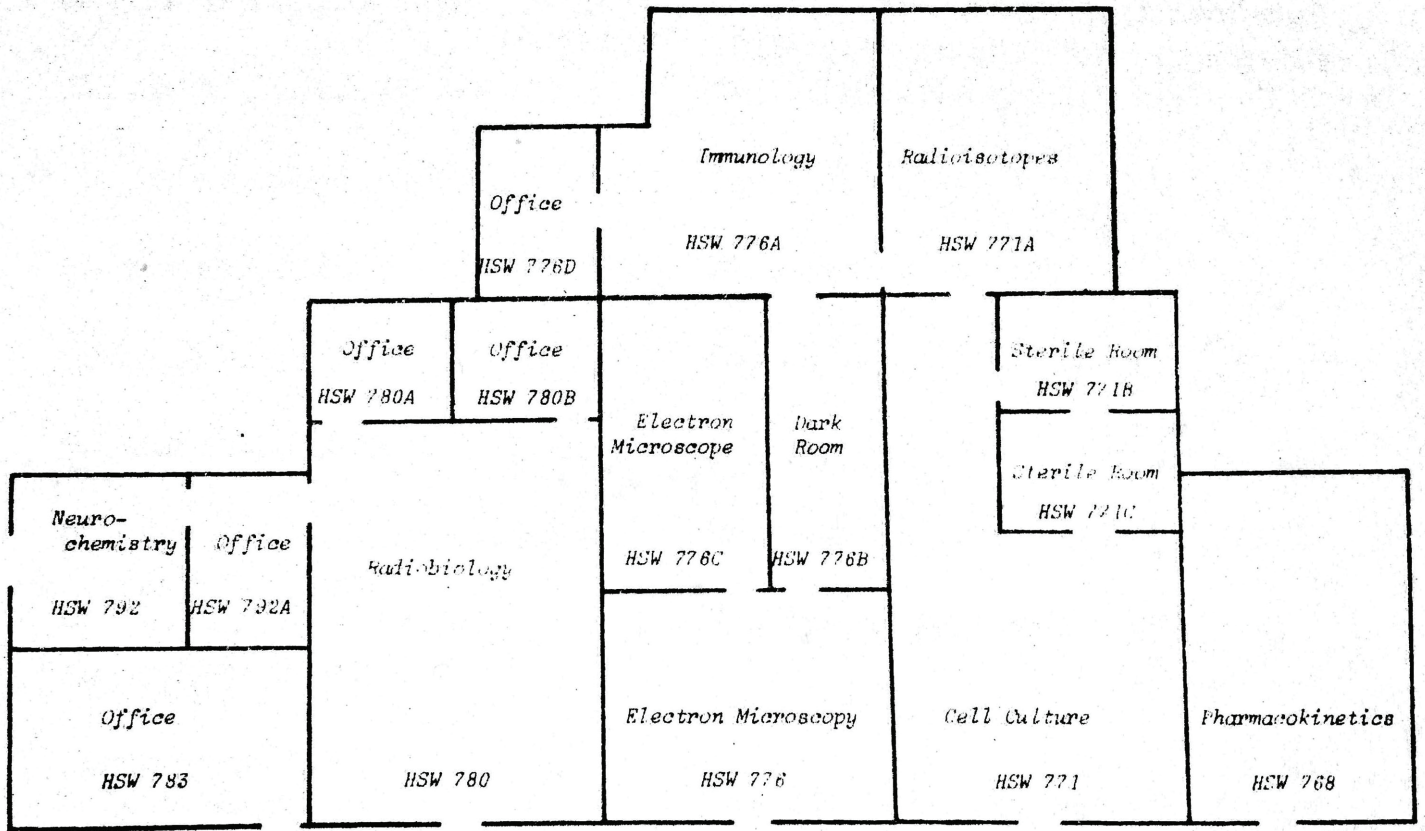
Layout of the library and offices on the 7th floor of the Science Building. Opposite: Layout of the Howard C. Naffziger Laboratories for Neurological Research. Construction of the lab facility finished in 1968 and the dedication ceremony occurred May 6, 1970.



On May 6, 1970, a group of speakers gathered on the sixteenth floor of Health Sciences West and addressed an audience. Charles Wilson was the first to speak.

“ Dr. Boldrey, Dr. Adams, and I shared Dr. Naffziger’s dream of an international center for neurosurgical research, and I am deeply honored by the distinction of serving as the first Director of the Naffziger Laboratories. In the titanic task of directing these laboratories in a manner that will sustain Doctor Naffziger’s unswerving standards of excellence, I am not alone, for I have an exceedingly capable group of associates. I am confident that we will bring the Naffziger Laboratories into a position of prominence. ”

Before touring the facilities on the seventh floor of the same building, Stuart Cullen, the Dean of the School of Medicine, J. Englebert Dunphy, the Chair of the Department of Surgery, H. Glenn Bell, Professor of Surgery and early Naffziger recruit in neurosurgery, and W. Eugene Stern, Chair of the Division of Neurological Surgery at UCLA and Naffziger’s son-in-law, all paid homage to Naffziger’s career and vision of neurosurgical research. But special attention was given to remarks made by another speaker at the ceremony, John W. Oswald, Executive Vice-President of the University of California. Commenting on his personal friendship when Naffziger was a member of the Board of Regents as well as his personal friendship with Charles Wilson,



whom he knew at the University of Kentucky where Oswald was past president, Oswald added: "I might indicate that it is a particular pleasure for me to be here because one of the last pieces of paper to cross my desk for this meeting of the Board of Regents was the formal establishment of a separate Department of Neurological Surgery with Wilson as the first chairman."¹

The inauguration of the Naffziger Laboratories, celebrated in the year of the birth of the Department of Neurological Surgery, on what would have been Naffziger's 86th birthday, was cause for a good event, even as it took place in moments of turmoil on the campus. It was also the day that President Nixon announced that American troops

had been sent within the borders of Cambodia on a limited "search and destroy" mission. Student protests and unrest prevented the attendance of the Executive Vice-Chancellor of UCSF.

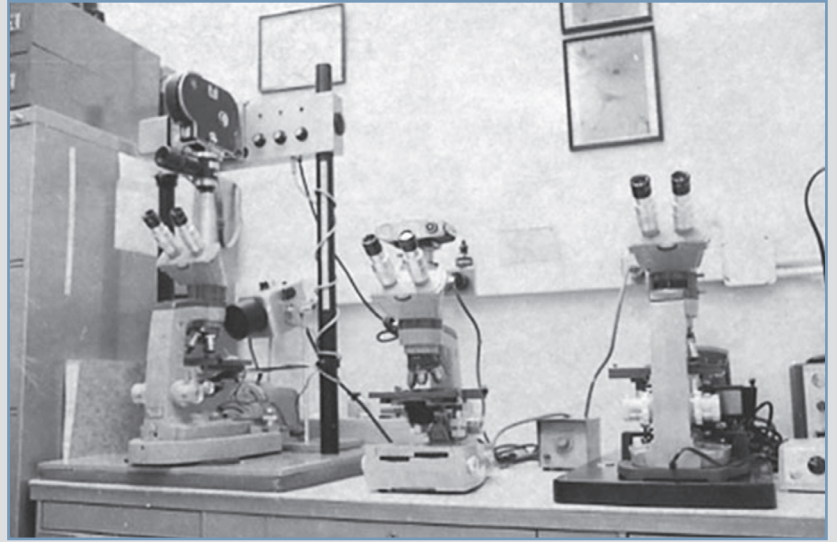
1970 was also the year that the "University of California, San Francisco Medical Center" was formally renamed by the Regents the "University of California, San Francisco," and UCSF became the new campus acronym. On many fronts, this was truly the dawn of a new era.

Below: UCSF faculty, students, and staff protest the US invasion of Cambodia, May 1970.





(A)



(B)



(D)



(C)

The Origins of the BTRC

When Wilson was appointed chair of neurosurgery in 1968, Edwin Boldrey was named vice-chairman. That same year the department was awarded a NIH training grant for a three-year period beginning 1969 to expand the faculty and support many phases of residency training, which was now a five-year program.

One of the first endeavors that Wilson and Boldrey launched was the Chemotherapy Program, which started in December 1968 with the introduction of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), which had been used in clinical trials since 1965. Over the following 18 months at UCSF, patients with recurrent gliomas, predominately glioblastomas, were accepted for treatment at the rate of approximately one patient a week. Working with advisors from the National Cancer Institute, the UCSF group evaluated the effectiveness of BCNU alone, or in combination with vincristine, intrathecal methotrexate, or imidazole carboxamide.

In 1969, with modifications made to the Naffziger Laboratories and the acquisition of equipment, two new major fields of experimentation were launched. The first employed cell culture and animal models as tools to investigate the biological nature of brain tumors and to implement the treatment of brain tumors by chemotherapy. The second encompassed surgical

and physiological problems related to neurosurgical techniques.

A look at the descriptions of some of the projects in the first two years shows the comprehensiveness of early investigations to tumor research and the range of collaborations.

Cell culture. The first brain tumor was submitted for culture in the Naffziger Laboratories in July 1968, and by the end of the second year they had cultured 80 specimens of different tumor types, from glioblastomas (the most frequent) to pituitary adenomas – over fifteen tumor types. The majority of glioblastoma cultures were studied in regard to their chemotherapeutic sensitivity, cloning capability, chromosomal complement, growth kinetics, biochemical requirements, histochemistry and ultrastructure.

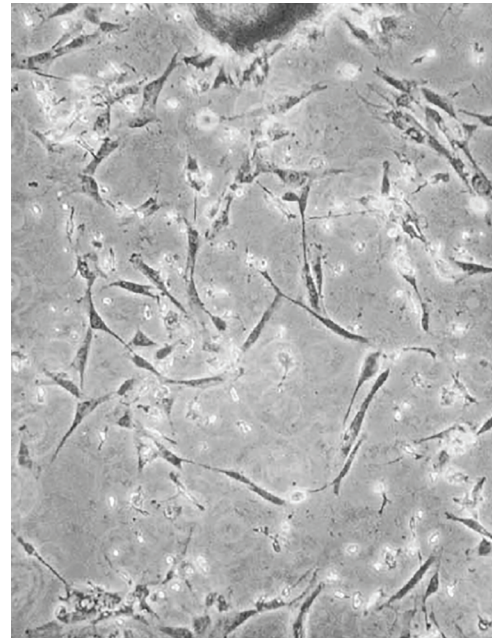
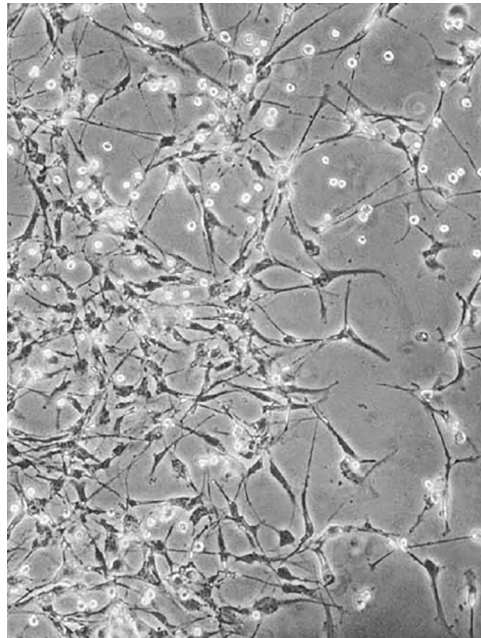
In vitro chemotherapy. Four potential anti-cancer drugs were assayed for their toxicity to cultures of brain tumors. A lethal endpoint for BCNU was determined against cell cultures of nine human brain tumors, and its toxicity compared to other compounds such as vinblastine sulfate.

Cloning. Experiments to ascertain the number of cell types involved in brain tumor formation. A glioblastoma in culture for five years was found to contain three distinct cell types – one type contained 52 chromosomes, while a second type, considered to be a giant cell, contained 104 chromosomes.

Opposite page: (A) John W. Oswald, as executive vice president of the University of California, giving a speech at the dedication ceremony for the Naffziger Laboratories in 1970. (B) and (C) Images of new lab equipment in the Naffziger Laboratories. Even though construction finished in 1968, the laboratories did not get stocked with necessary equipment until the following year. (D) From left to right: Stuart C. Cullen, H. Glenn Bell, John W. Oswald, Charles Wilson, W. Eugene Stern, J. Englebert Dunphy. These guest speakers, as well as Edwin W. Rosinski (not pictured) gave a speech at the dedication ceremony for the Naffziger Laboratories.

Left: Primary cell culture of fetal puppy white matter at 8 days, illustrating proliferation of astrocytes. Right: Primary cell culture of glioblastoma 253 at 8 days, illustrating neoplastic astrocytes. A fragment of the explant appears at the upper edge of the field.

Images featured in "Studies of malignant brain tumors in cell culture" by Charles Wilson and Marvin Barker, Annals of the New York Academy of Sciences, 1969.



Chromosome analysis.

Chromosome analysis in conjunction with morphology was the major criterion for determining cell types.

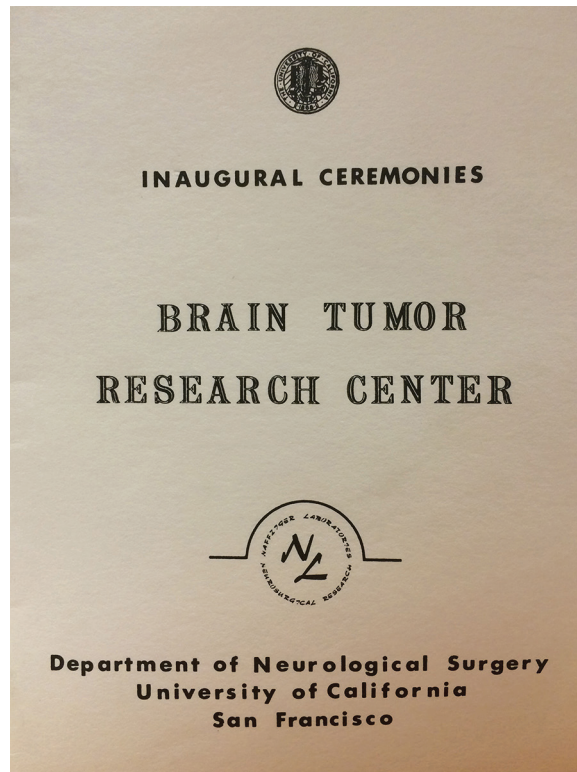
Cell population kinetics.

Autoradiography was used to determine the generation time of cultured brain tumors. While the generation time of cultured gliomas was still to be determined, rat gliomas were found to have a doubling time of 18 hours, which was much faster than the generation time of 24 hours determined for human brain tumors using cinephotomicrography.

Animal model for brain tumor chemotherapy. The research group obtained a chemically induced rat glioma from Massachusetts General Hospital that grew well in cell culture and, upon stereotactic transplantation to the rat brain, produced a typical malignant astrocytoma. Testing with BCNU showed a significant increase in the survival time of affected rats.

This is only a sampling of the range of experimental inquiries that were launched in the new labs. Also investigated were surgical techniques, experimental lesions in peripheral nerves resulting from contusion, intrathecal cold saline injections for treating intractable pain, and the evaluation of methods of producing aneurysms in femoral and brachial arteries in animals.

Since the inception of the chemotherapy program, referrals from neurosurgeons in northern California had led to treatment of 239 patients over the course of its first few years. A chemotherapy nursing program was established to coordinate treatments and patient care and a chemotherapy fellowship started, which allowed junior surgeons to move between the lab and the clinic, facilitating a rapid translation of knowledge



Program cover for the BTRC inaugural ceremonies.

from bench to bedside.

Altogether the Department showed significant growth in the early years of Charles Wilson's chairmanship. Now there were twelve full-time faculty, eight residents, eighteen faculty and research associates at the Naffziger Laboratories, and an additional forty-two clinical faculty.

By 1972 three major grants had significantly boosted the finances and activities of the department. A Postgraduate Training Grant for \$365,118 was awarded for a five-year period effective July 1972, which provided salary support for the faculty as well as stipends for residents during their period of laboratory research. A \$125,000 award from the National Institute of Neurological Diseases and Stroke was received by PI Julian

Hoff to support clinical and laboratory research on the physiology of cerebral blood flow and intracranial pressure. And finally, the National Cancer Institute provided a \$759,000 grant to establish and support a Brain Tumor Research Center for three years from 1972 through 1975. The last award began the program that would become the largest brain tumor treatment program in the nation, and used a model of organization for translational research. The letter that Wilson wrote to William Hammond, awards officer at the National Cancer Institute, dated September 17, 1970, which initiated the BTRC, was kept by Wilson and reproduced in the following pages.

UNIVERSITY OF CALIFORNIA
SAN FRANCISCO MEDICAL CENTER

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SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE

SAN FRANCISCO, CALIFORNIA 94122

September 17, 1970

William G. Hammond, M.D.
Clinical Investigations Branch
Extramural Activity
National Cancer Institute
Room 10A03, Westwood Building
Bethesda, Maryland 20014

Dear Doctor Hammond:

Pursuing our conversation in Los Angeles, I want to convey my thoughts concerning the evolution of a Brain Tumor Research Center at the University of California, San Francisco.

First, I should say that the concept of a Brain Tumor Research Center has an enormous appeal since, in fact, we are presently functioning in that capacity. I will describe our present activities, including what I would consider desirable in three areas: clinical chemotherapy, research and training.

1) Clinical Chemotherapy

An active clinical chemotherapy service requires an adequate volume of patients, a sufficient number of hospital beds, personnel committed to the project, and adequate supporting personnel and facilities. During the past 20 months we have accepted approximately 100 new patients on four phase-2 protocols (BCNU, BCNU plus vincristine, intrathecal methotrexate, and CCNU). In addition we have participated in a phase-3 study in cooperation with the NCI-sponsored Brain Tumor Study Group.

Personnel working exclusively on the project include a chemotherapy nurse (Jean Enot, R.N.) and a chemotherapy fellow (Derek Fewer, M.D.) who is a third-year resident from the Montreal Neurological Institute. Two members of our staff, Doctor Edwin B. Boldrey and I, have a long-standing interest in brain tumor chemotherapy and a firm commitment in this regard.

Supporting personnel and facilities include: a) Neuroradiology (Hans



2

Newton, M.D.); b) Neuropathology (Nathan Malamud, M.D. and Surl Nielsen, M.D.); c) Nuclear Medicine (Malcolm Powell, M.D.); d) Neuro-ophthalmology (William F. Hoyt, M.D.); and e) Radiation Therapy (Glenn Sheline, M.D.).

2) Research

A brain tumor research program should be broad-based and cover areas such as animal tumors, carcinogenesis, biochemistry, ultra-structure, cell population kinetics, and immunology.

The Howard C. Naffziger Laboratories for Neurosurgical Research were dedicated in May of this year. The major thrust of our research efforts involves various aspects of human and animal tumors. Three investigators hold academic appointments: Yoshio Hosobuchi, M.D., who is in charge of the electron microscope laboratory; Marvin Barker, M.S., who is in charge of cell culture and animal models; and myself. At the present time, four postdoctoral fellows are engaged in brain tumor research assisted by five technicians and three medical students. Our present activities include cell culture, determination of amino acid requirements of neoplastic glial cells, gas-liquid chromatographic analysis of disordered steroid synthesis in glial tumors, electron microscopy, tumor induction, tumor cell kinetics in vitro and in vivo (both rat and human), immunology, and a variety of experiments utilizing transplantable rat gliomas.

3) Training in Clinical Chemotherapy

Doctor Derek Fewer is now spending 18 months as a chemotherapy fellow. We hope to continue and expand the training program and will accept neurosurgical residents with two years or more of training or after completion of training. Our present program includes both clinical and research responsibilities. Since Doctor Fewer joined us in July of this year, the program has been in a rapidly developing stage of evolution.

The curriculum for the trainee includes the following activities, most of which have been in operation for at least one year.

- a) Cancer Research Institute - Throughout the year the Cancer Research Institute (CRI) sponsors lectures for faculty and house staff. In addition, the trainee will attend weekly rounds on all patients in the CRI under the direction of the CRI staff.
- b) Cell population kinetics - Doctor James Cleaver, author of a recent monograph on thymidine metabolism, and

3

Dr. Harvey Patt, Director of the Radiobiology Institute, give a series of basic lectures and conduct bi-monthly seminars in which we discuss current literature as well as research in their laboratories and in our own.

- c) Nuclear Medicine - The trainee attends the daily reading of all brain scans and independently evaluates serial scans on all patients under treatment.
- d) Neuroradiology - Doctor T. Hans Newton conducts a review of neuroradiologic studies on neurosurgical patients three times weekly. This conference includes interpretation and comparison of serial studies on chemotherapy patients.
- e) Pharmacology - We are setting up a bi-weekly seminar in pharmacology under the direction of Doctor Kenneth Melmon. We will discuss basic pharmacology as well as the pharmacological properties of new oncolytic agents.
- f) Basic Science Lectures - Throughout the year weekly lectures are given by members of the faculty for residents and graduate students in the neurological sciences. Subjects include neuropharmacology, neurophysiology, neuropathology, neuroanatomy, etc.
- g) Neuropathology - Weekly gross brain cutting is conducted by Doctor Nathan Malamud and Doctor Surl Nielsen. Doctor Boldrey and I hold a weekly microscopic conference in which we review all neurosurgical material from the previous week.
- h) Immunology - We have just submitted a grant proposal involving immunologic studies of patients with neuroblastomas, medulloblastomas, retinoblastomas, and neurofibromas. This proposed project is a collaborative effort with Doctor Hugh Fudenberg, head of our Division of Immunology. As this work evolves, we will participate in weekly seminars with Doctor Fudenberg and his staff to discuss current research in his laboratory as well as a systematic review of tumor immunology.
- i) Radiation Therapy - We hold informal conferences with Drs. Glenn Sheline and Theodore Phillips regarding 1) all new patients being considered for radiotherapy including review of radiographs, operative findings, and pathology (Decisions regarding parts and dosimetry are made at this time.) and 2) radiotherapeutic data on recurrent tumors referred for chemotherapy. (All are reviewed in respect to adequacy of prior radiotherapy and the possibility of radiation reaction as opposed to tumor regrowth as the basis for the patient's neurologic deterioration.).
- j) Research Meeting - I hold a weekly meeting with all laboratory

Image on opposite page: William G. Hammond, MD, awards officer at the National Cancer Institute and professor of medicine in the Department of Surgery, Peter Bent Brigham Hospital, Harvard University.

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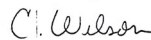
personnel at which time we review work in progress and offer group criticism of presentations by each member of the research team.

- k) Chemotherapy Rounds - I make rounds with the trainee three times weekly. Once weekly we have grand rounds on all chemotherapy patients, this activity being conducted by Dr. Boldrey and myself and attended by resident staff and interested persons.

I am excited about the possibility of obtaining broad-based support for a program such as the one outlined. I am eager to discuss this with appropriate persons and I would welcome a preliminary site visit in this regard. If I can furnish any additional information or elaborate on any point I would be more than pleased to do so. I appreciate your interest and I do hope to hear from you directly or indirectly in the very near future.

With kindest regards.

Sincerely,



Charles B. Wilson, M.D.
Professor and Chairman
Department of Neurosurgery

CBW/bp

Charles Wilson (right) talking to Maurice Smith (left) and Carl Pevehouse (center) at a departmental party celebrating recent graduates of the residency program in 1969.



The inaugural ceremonies for the BTRC took place January 7, 1973. From the windows of the glass tower of Health Sciences West guests could look down on the structure of the Old Medical School building that was, that same year, demolished, forming the space that is now the quad. A symbol of the disappearance of old systems of medical knowledge being replaced with multidisciplinary approaches to the diagnosis and treatment of diseases.

This captured the goals of the BTRC. The clinical research program evaluated promising drugs as an institutional member of the Brain Tumor Study Group of the National Institutes of Health. It also aimed to design new therapeutic regimens by taking advantage of knowledge gained through laboratory research on tumor kinetics and pharmacological properties of drugs and irradiation. It engaged investigators from biochemistry,

pharmacology, immunology, radiobiology, and virology, among other basic sciences. The BTRC rode the momentum of scientific advances nationwide and in departments at UCSF in cancer research. Progress was being made in the treatment of acute childhood leukemia, uterine cancer, and Burkitt's lymphoma. Extensive studies of drug transport, absorption and action had clarified the uses and limitations of current agents and indicated the essential requisites of new drugs.

The BTRC became the first concentration of scientific effort on tumors of the central nervous system. The achievements of the investigators of the BTRC are well documented. Faculty members who were at UCSF when Wilson arrived and witnessed the growth in research and service observed the crucial steps Wilson took to help the department push back the frontiers of knowledge. To Grant Gauger, who met Wilson in 1968 as one of the first neurosurgical

residents interviewed for admission by Wilson, he proved to be “a remarkable man of boundless energy and activity.” In the judgment of Robert Weyand, a long-standing member of the department who was one of the last to perform surgery with Naffziger, Wilson was “the premier guy—an incredible technician.”² When Wilson first arrived in San Francisco and articulated his ambitions, Weyand worried about the challenges Wilson might face. “But,” says Weyand, “he reached out to people in different functions and specialties very effectively.”

The emphasis on Wilson’s communication skills was echoed by others, who saw also his commitment to fostering collaborations with other departments as well as other neurosurgeons to enable UCSF to become an important center for referred patients. Wilson believed that UCSF “needed to provide great clinical care and research in order to contribute to the forward movement of neurosurgery,” said Lawrence Pitts, who finished his residency under Wilson in 1975 and went on to have a distinguished career at UC, becoming Chairman of the Academic Senate and retiring as provost. According to Pitts, one of the strengths that started to emerge early in Wilson’s tenure was his eagerness to hire strong neurosurgeons without much concern about whether he could “control” these people. “Wilson was happy to hire and support faculty members

whose interests and skills went beyond his personal purview. He had a view of what made someone a strong faculty member; this was a good clinician who could present well to the public as well as someone who was interested in contributing to the next chapter of neurosurgery’s capabilities.”³ Wilson hired faculty who he thought would be strong clinicians, good with people, and able and willing to launch (and oversee) research programs in their fields of interest. “Wilson never met a referring physician he didn’t like,” Pitts said. Wilson believed that one of the best things for UCSF was for all faculty to be available to referring physicians. “This is how UCSF started to become a referral center for neurosurgeons around the country, which is exactly what you want an academic department to be,” said Pitts. UCSF became a place where such doctors sent their difficult and unusual cases. “You want other physicians to say, ‘If I had your problem, or if my mother did, I would go to or would send her to UCSF.’ You want to create collaboration between UCSF and the referring physicians with the common goal of the best outcome for patients.”

Reflecting on thirty years of history, in 2006 Charles Wilson was interviewed by faculty in the Division of History of Health Sciences at UCSF, which provides a personal perspective on these achievements.

An Interview with

The Creation of the Brain Establishment of Translational

By Dorothy Porter, PhD

From the time that he was appointed as the first professor of neurosurgery at UCSF in 1929, Howard Naffziger aimed to integrate clinical practice with laboratory based experimental neurological research. Naffziger was a student of the 'father' of neurosurgery, Harvey Cushing, and was therefore trained in the school of thought which believed that as a sub-discipline of medical neurology it required continuous commitment to experimental neurophysiology. As a result, a professional and intellectual culture was established in the division of neurosurgery under Naffziger in which clinic experience informed and was informed by experimental laboratory science. In this respect the research culture within neurosurgery under Naffziger mirrored the later conceptualization of bi-directional translational research that was later to be developed by Samuel Broder.

The culture of bi-directionality significantly expanded when Charles Byron Wilson joined UCSF and transferred his laboratory in which he was studying the basic biology of brain tumors from the University of Kentucky in 1968. Frustrated with the low survival time of patients who had received surgical and radiation therapies for malignant brain tumors, Wilson began exploring chemotherapeutic possibilities from the early 60s. He started his brain tumor laboratory when he was appointed at Kentucky in 1963 but when he transferred them to UCSF Edwin Boldrey, Chairman of Neurosurgery, was also developing a clinical research program. The collaboration between the clinical and biological research programs in brain cancer that developed after Wilson's arrival was significantly facilitated by Wilson's continued innovative surgical practice. After joining the neurosurgery department Wilson developed his transsphenoidal surgical operation for pituitary tumors, which he eventually practiced successfully on over 3000 patients by the time he retired in 2002. Wilson, like DeVitta and Broder at the National Cancer Institute, was a physician-scientist and

Charles Wilson

Tumor Research Center and the Research in Neurosurgery at UCSF

this informed his nurturing of clinical and basic science collaboration in the development of the Brain Tumor Research Center at UCSF.

In 1970 Berthold and Belle Guggenheimer and Charles Kaeding provided endowments for the establishment of new Howard C. Naffziger Laboratories for Neurosurgical Research at UCSF, which gave Wilson the chance to establish a multidisciplinary research program to seek effective treatment and ultimately a cure for brain tumors. The Naffziger labs employed a wide spectrum of the basic sciences including cell biology, cell kinetics, cell culture, radiation biology, and pharmacology and experimental therapeutics. The correlation of data derived from the clinical and laboratory programs provided the means of rapid exchange of information among investigators that had a synergistic effect. The expertise involved in this multidimensional approach included clinical and basic science faculty from many departments within UCSF's School of Medicine fostering a translational approach that built upon the collaborative culture initiated by Naffziger.

The following are excerpts from a previously unpublished interview conducted in 2006 by Dorothy Porter, professor of history of health sciences at UCSF, as part of a study into the early development of translational research programs and the conditions of successful collaboration between physicians and scientists in developing novel therapeutics.

Wilson: My first recollection of ever hearing the word [translational research] was in reference to the Brain Tumor Research Center and it came from the NCI. They said UCSF is a model for translational research and that word had great implications. I think the best decisions we made were what things not to get into [just] because there is this discipline of the day that is going to be able to help us solve our problems—immunology is one. And so you study the field, see what's going on, see what its future is, see how it fits in with what else you were

doing, which was largely chemotherapy at that time and still is. If you place too many bets just to have yourself in play, it's not a very good strategy. So strategy is deciding what not to get into and then it becomes much easier to understand what you should be doing, where's your strength and how can you augment that.

I was trying to think of a metaphor for what the [BTRC] was like in those 20 years. I had described it to the NCI committee as, we're almost like a family. And I don't think that was really the best. We were more like a community. I don't know whether you've read the book, *The Wisdom of Crowds*? Read it, it gives you insights that you can't believe. And so we fulfill the model really of the *Wisdom of Crowds*. We were very diverse: lab techs, researchers, secretaries, neurosurgeons, residents, fellows. First thing, we were diverse. Secondly, we were largely independent in a sense that there were no dumb questions and sometimes you learn a lot from the people who ordinarily are muted in an audience where they are not with their peers. And so it was independent. Thirdly, it was not centralized in a sense that I was in any way a micro-manager. People ran their own labs independently. All I wanted was to know that I had the best people there and support the talent I had. And the final, fourth point with the *Wisdom of Crowds* is a way to aggregate this collective wisdom.

Interviewer: I was wondering if I could ask you to explore a little bit more how you said that you were interested in who you've been working with, people who had the same passion and energy. And I'm wondering how you were able to both recognize that and then channel it into this focus on the single goal? You know, people coming from different disciplines?

Wilson: Oh yes, absolutely. There are people whose eyes light up, they see this as a problem, often they're into radiobiology, let's say, Dennis Deen, for example. He actually came as a fellow, but he became interested in brain tumor as an opportunity to work with someone who is doing exciting things. And how that goes, the word gets out. It's like having brand equity. You want not only people who are loyal and buy your product, you want people who recommend your product.

So it just works! Everybody likes to get on the moving train. Things were happening. We were growing. We're doing good things, and I certainly discount my leadership as that. I just happened to be in a position where there were a lot of bright people and it's just a matter of them self-selecting or being selected because they, in some way, would complement your quest to reach your goal, which was to cure malignant brain tumors.

So every month we had lunch together and every week we met with everybody including visitors if they wanted to come along. Often it was patients' families. We had a patient in the hospital, we'd invite the family, we're

having a research meeting, would you like to sit in the back with us? If you have any observations you like to pass on, please pass it along. But we want you to know what we're about. And then you could say, well, that was just absolutely openly soliciting the contributions! Nothing of the sort! It did, but that's secondary level. We thought it was important for members of the public, particularly now that they had a brain tumor in the family, to be exposed to it.

So it was this common goal, or mission, it was community knowledge or group knowledge, so they knew why they were doing the experiment and they could come up with an observation -- well you know we're doing this as [self-culture] and almost by accident we discovered this. Bam! Maybe it's going to click and someone said we ought to look on that, maybe that is the basis for pursuing this and basically ending up at the clinical trial. And if you take the really landmark things we did, it was sort of like that. First drug, BCNU, still used today around the world, which is sort of a sad commentary. And then using drug combinations, which was at the time used in Hodgkin's disease, very little else. Reducing the dose of radiation in childrens' spines, [for kids who] had a certain kind of tumor. You've got to have a clinical arena for the laboratory where you have enough volume that you can conduct this as a single-institution trial. Although I was involved in the first brain tumor study group, one of the founders, and still participated in and actually helped developed ideas in trials for them. But still we were running our own operation because they were so tightly controlled. We weren't depending on a bunch of co-investigators who might or might not do things the way you did, for instance their radio-therapy might not be up to our standards. And we learned a lot about that.

Interviewer: I'm intrigued that you clearly set out early how to maintain this idea that clinicians and lab had to be really working hand in glove, you couldn't successfully get to where you want to get within the separate enterprises. That must have been somewhat unusual when you began the work?

Wilson: Well I had begun in research as a medical student, yes as a freshman in medical school.

Interviewer: Can I ask you a question about that - I was wondering whether you ever consciously felt any influence from the "father" of neurosurgery, Cushing, who had a philosophy that you couldn't undertake neurosurgery without investigating the biology of the brain and the biology of the --

Wilson: Yeah, well, he was ahead of his time.

*Charles Wilson,
MD, in 2011. Photo:
Brant Ward, San
Francisco Chronicle*



Interviewer: And it seems to me that what you did was really take up that philosophy and realize it in the BTRC. I was just wondering whether that was any influence on you?

Wilson: Well I think it was. As an undergraduate, I belonged to the History of Medicine Society and I gave two reviews. We met periodically - I think every month or two months—and one was the Biography of Cushing, and the other was Cushing's Biography of Osler, for which he got a Pulitzer Prize. So, there was this curiosity or it was just something that you like, now very often it's done because it looks good on your application of medical school, wherever. The residency itself, I think is a separate issue.

We want to train at UCSF. We think we have such an array to offer that we really attract, and I've been totally open about for 15 years, people who have the potential, who know they want to go into academia. And academia doesn't mean you're going to have a research lab. It adds a great deal to the way you look at every patient and every problem. That, of course, is another way to do it – translational research team of one. We have some examples of that where they are focused enough that it can be applied.

Interviewer: The questions that were provoking, the questions that you were investigating in the laboratory, those questions emerged as you said within a surgical environment. One of the problems currently, I think, with translations

such as that. The basic scientist, because of the lab and their [tentative] award has become to separate it intellectually as well as physically in modern hospital that sometimes basic science operates in isolation from the clinical experience.

Wilson: Right.

Interviewer: So you think somehow institutions have to structure an environment so that clinic is constantly feeding back into the laboratory.

Wilson: I think that's wrong. Remember *The Wisdom of Crowds* - diversity and independence, so they have a choice. We may present a clinical problem and it clicks because they too want to be on the stand waving banners the day we can cure malignant brain tumors. Now, science for science sake, let's say. Mike Bishop discovered oncogene. Was that translational research? No, it wasn't. But did it end up eventually that knowledge being translated by people who realize the power of genomics. And I had one of my residents spend a fellowship with Mike and another one in a laboratory where we were looking at very early receptor cells because they truly inform them to give them the understanding to ask the question, or use that in solving the problem. So absent the knowledge of that exists, you don't make these connections. Well, maybe brain tumors of this kind – we looked at the receptors and who's doing it and at UCSF somebody is always doing something. So that's one of the joys of the whole culture of UCSF, it's absolute open movement between basic science and clinical science. You know, we've grown, basic science has grown, they've grown, we've grown, because they were part of what UCSF was all about.

Interviewer: It strikes me that these weekly luncheons that you had were probably a very important forum for ensuring that transfer of knowledge between people, or no?

Wilson: I think less so than just being together. Everybody knew what was going on clinically, clinical trials, periodic report and we knew what was going on in the labs. And the different labs would collaborate with each other. So it was free flowing information ideas that just set off a spark. But I don't know if the translational research that began in the BTRC would have happened in the way it did and with the speed it did in another institution. I've said that looking back at my own career, there was never any ceiling on what I could do. What I could do is what I was able to do, I was not constrained by my institution. And I often tell residents looking for a job that what they ultimately are able to accomplish, professionally, will be limited, by one thing and that's the institution that they're in and the people with whom they interact. And UCSF is a prime example of that, because when you can pick up the phone and call somebody by first name and say, "Who's doing this?" "Well, someone's going to this lab, well, give them a call." Most places you have to

get on the phone, go to someplace else and find out who the experts are, or to be informed by an expert on who the other experts are. So the first time the term [translational research] was used was in reference to what we were doing. Were other people doing it to that extent? Not to the extent that we did.

Interviewer: Back to your earlier comment about you weren't a micro-manager. I'm wondering where did your leadership style come from and is that something that you've been looking to sort of find in other personnel?

Wilson: Well, either you're a micro-manager or you're not. It's in the genes, it's in your past, but I think it has more to do with my upbringing. A little bitty town, 5,000 people, rural Missouri, big dairy country—your honor was the most valuable thing you had. And if you lost it, you lost it—and you never get it back. A handshake, we didn't need a lawyer or legal document, if you trusted someone, because you knew they wouldn't go back on their word, because they would be—we'd say back then—tarred and feathered! ... It's created some problems with me in my life. I've been badly screwed by people whom I trusted, but I never changed my colors. I would prefer to trust people, if I think they are trustworthy, and if you've read Malcolm Gladwell's book *Blink*, I think you can establish that very quickly. It isn't without, as Malcolm points out, its liabilities because we can be misled by the wrong impression and I've learned from that.

So if you trust people, you're going to support them and then you don't look over their shoulder. You want to be informed but you don't want to be controlled. Now, what characterizes a micro-manager—insecurity, lack of trust, you know on and on. And I was certainly secure, not arrogant or above criticisms of many sorts, but I did have the confidence in what I was doing and what I was doing it for. So, there is a reality to it. Someone is not doing good work, they're not going to be funded, but that's a message. And sometimes, it's not their fault. It's the same way I ran the department. Everybody in the department had a job. They represented me. They could make decisions in my name, committees and that at UCSF, so everybody had something. And it was at the same time, giving them a practice, a vision or a feeling for what it was like to be an administrator. And as they got more senior, they got more senior roles, representing me on the medical board, hospital or whatever, there were countless meetings. You're going to make some mistakes but don't make any big ones — and I'll leave that to your judgment.

Interviewer: The issue of trust in team science is a very interesting thing.

Wilson: Oh! Absolutely.

Interviewer: It just comes back to something that I'm especially interested in, which is different cultures of curiosity in different models of science. And one

of the ways in which, perhaps, it's hard for clinicians and basic scientists to intellectually synergize what they're doing, is to do with a lack of understanding which leads to a kind of lack of trust of each other's model of science. So it's interesting that you seem to be saying that the BTRC provided this environment, in which sort of intellectual trust emerged. Is that a result of all this interaction of basic scientist being in the clinic and clinicians actually working side by side.

Wilson: We'd have picnics, tennis, volleyball and stuff. That doesn't make a team but getting to know people can establish trust. And by their actions, in a very short time, they're trustworthy or are they are trying to steal my data, whatever it is. Trust is very important and I've studied great teams. What are the great teams—the Yankees it was a great team. Diverse? You bet. Trust? You bet.

Interviewer: Unless you allow trust to flourish, you can't turn independent into interdependent.

Wilson: No. You can't just aggregate it and come out with something. ...

Interviewer: If you were to evaluate a [CV] of a post doc, resident or scholar of some kind, how important is it to you that you had maybe some connection or some sense who their mentors had previously been—how did you evaluate this quality in the people that you were --

Wilson: They have a yearling sale in Lexington, Kentucky. You can look at the pedigrees, tells you something. But if you want to see them run, you want to see them run. So do you hire somebody based on that? I think that's a little risky. Number one, they have to understand the culture, if they're coming in. They have to meet other people and those other people have some input—is this person right for us? I mean you can pick out somebody coming from Harvard and we've got letters that you'd kill for. And they come out and they see everybody, they go have dinner one night with the residents. We call in the secretaries, residents, faculty, and we say, "What did you think of them?" I think once you've established what we're about, the culture, it is self-attracting, self-repelling, on both sides. The superstar coming in, they say, "You know it didn't look like they wanted a superstar, they just want somebody to get on with what they're interested in doing." I mean that's taking a very narrow view. But they are self-repelling or self-attracting.

Interviewer: So researchers have to have sufficient independence to achieve excellence but also must feel that they're part of the community. So the purpose for achieving excellence is to benefit the team.

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Wilson: Right. It's not just for excellence itself.

Interviewer: Can I ask you another question I think really critical to this which is about technology. I know that you're an enthusiast for the role of technology and transforming the future of medicine. And can I ask you to give your reasons for that, why you think technology is so important to transforming and how is it going to transform medicine. What's medicine is going to look like in 25 years time?

Wilson: I can tell you 10, but not 25. Why technology? Well, technology embraces two things. It embraces technologies as we usually think of them, drugs, devices, so forth. In fact there's a list of some 31 that we look at in the Health Technology Center, but it also includes processes. They are a technology, by definition. So, if we don't get any new tools, i.e., technology, devices, drugs, and if we don't have any new processes, what's going to change? So they become self-centering, because technology needs to be applied. And that's why we spend so much time with technology assessment. Is this an advance? Does it say it's an advance? I've written an article on the adoption of diffusion of surgical technologies and how that is done and how spaces are made because questions aren't asked. One example is something that's really the rage, going at 20% a year, and I predict its demise because they have never done a clinical trial. So what's the message, today it's called evidence-based medicine. And, there's a new kid on the block and he/she is talking about cost effectiveness, analysis and you've got your own experts here on that. Because it's one of the reasons that things are out of control. So, we have these ways of judging it and the mission or goal, to the Health Technology Center is to encourage the adoption of technologies that benefit health, period. And if you stick to that and it's gone through the filter because we can improve health or a population, and that's how we have to think. It's not democratic, you know, I will do everything that will be of any benefit to you, as long as the two of us shall live. We have a family to feed and we can't send the two boys to Harvard and have the girls going to the Food Kitchen — something to that effect. It's a responsibility of this country, this government, to be sure there's equitable distribution to the point that there is a floor and you establish floor to ceiling. But to establish a floor that is the right of every American and everyone within our shores who does not have evil attempts — you can see I'm just a bleeding heart liberal.

Interviewer: Would you say that this seeking of new technology, the development of new processes, is that another way of ensuring diversity so that you have the tools and the processes that best fit a particular situation?

Wilson: Well, what happens—two technologies, one here and one here advance but they advance only so far. Here is the third technology that is

Personality

Dr. Charles Wilson - Finding a Cure for Brain Tumors

an Herbert
Charles Wilson's life is to finding the cure for brain tumors. He has given this as challenge his time and since he finished medical 30 years ago.
hoping to live to see the "cure" for brain tumors," said. "But now that I'm in it, I'd say I'd better hurry."
hurry. The 62-year-old chair of neurological and director of the renowned Research Center at Moffitt Hospital is working on from all angles — even helping plan the first fund-raising drive for the center.
nately, Wilson has the whatever it takes. "I've always had more than my energy," he said. "And, absolutely adore what I do."
Wilson finished his training at Tulane in New Orleans in 1960 and his lifelong interest in brain tumors.
s the most depressing and I knew that's what I was doing," he said.

program, Wilson is also one of the foremost educators in his field.
Of medium height, physically spare, with buzzed hair and a ready smile, Wilson took a deep breath and disengaged himself for an hour from a demanding day to discuss his work and the center's financial needs.
At one point, he paused briefly, reached into a desk drawer and applied lotion to his hands.
"My hands and my eyes are pretty essential in what I do," he explained. He doesn't count the number of surgeries he performs each year but guesses it's somewhere between 150 and 200.
Heading a staff of more than 50 health-care professionals and researchers, Wilson oversees the largest brain tumor clinic in the country, treating approximately 400 new patients with brain tumors each year.
One wall of his office at Moffitt Hospital is papered with framed honors, awards and certifications. Mementos from the academic trail and from patients and colleagues are sprinkled among shelves of books on another wall.
Charts and models of brains are alluded to during his meet-

you are going to beat the disease, you have a better chance. If not, you're dead in the water."
That same hope fuels Wilson's determination to find answers.
"Patients are doing better now; there are more cures today," he said. "Some tumors that 25 years ago people agreed were universally fatal are now curable."
There are many different kinds of brain tumors, occurring in different parts of the brain. Some are benign and some easily treatable by radiation therapy. Getting the research attention now are the astrocytomas, the tumors that invade the brain with tentacle-like growth.
No longer are researchers thinking of tumors as lumps, but rather defining them in terms of individual cells — how they proliferate, why they get out of control.
"Research is so expensive," Wilson said. "It's not a couple of rats in a cage anymore. Our annual budget is fast approaching one million and that's not including clinical staff."
Funded by government grants from the National Cancer Institute and the American Cancer Society,



Dr. Charles Wilson, M.D., says he hopes to live long enough to see all brain tumors curable. Wilson will appear on the show "Night of Entertainment" on Monday, Nov. 11, at Davies Hall. The star-studded show will feature Burt Reynolds and friends. For further information, call 296-1111.

San Francisco Chronicle
PEOPLE



Dr. Charles Wilson performs one of three brain operations in a morning at UCSF. "I got good results," he acknowledges. "I think it's intuitive."

The Baryshnikov Of Brain Surgery

Charles Wilson of UCSF is called by patients and peers the world's top neurosurgeon



A colleague calls Wilson, 62, "one of the two or three most influential people in our field in the world."

BY SAM WHITING
CHRONICLE STAFF WRITER
The beautiful woman walks into Dr. Charles Wilson's small office at the University of California at San Francisco, followed by her parents on a hot Thursday morning. The woman is 29, in good health until a frightening instant months ago when she couldn't understand what her three children were saying.

running through his veins," he says if forward, "but I can't allow myself to get caught up in the agony. I'd have to take the rest of the day off."
There is no time for that. He still has 10 patients to go and this is his slow day.
"Good morning, doctor," says the next visitor, a middle-aged man from Florida on a non-operative visit. "I want to thank you for seeing me."

feel for what to do next. It's a gift. Just a damn gift."
This has been recognized early and often by both peers and patients.
"He's probably one of the two or three most influential people in our field," says surgeon Hal Hankinson, M.D., president of the Congress of Neurological Surgeons. "He's known everywhere that neurosurgery is done."

sort of stalled and sputtering, but now Moore's law, we have computational power and let's plug it in and it enables this technology to flourish because now we have, with this computational power, we can do things like the Internet, Broadband, send videos and so forth. So there's many examples of this, and this is one thing we do at the Health Technology Center.

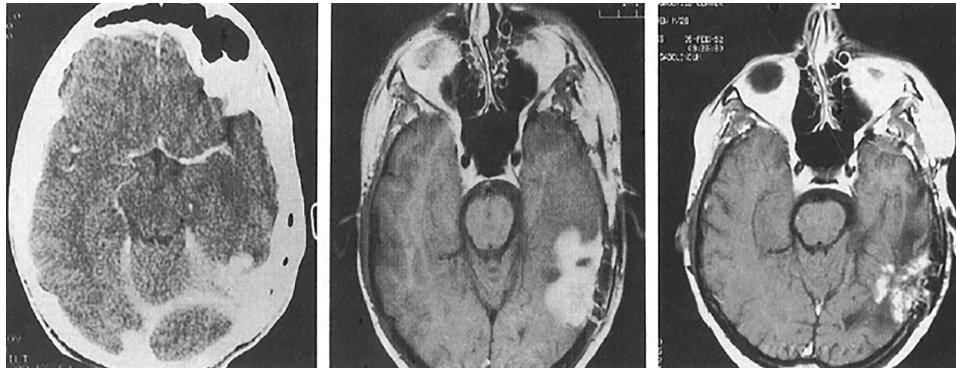
Interviewer: Think you'll cure brain tumor disease?

Wilson: I said boldly, I think it was 1970, "I will see the cure of malignant brain tumors in my lifetime." But I'm 77, I'm going to say, "Hurry!" Yeah, hurry, I don't want to make a liar out of myself. I can remember where it was happening, it was in Louisville, and there were eyeballs rolling. But I actually believed it. We had just seen BCNU and the power it had and I was pumped. I was really pumped.

Interviewer: Do we have a better handle on causes of brain tumors these days?

Wilson: Genes is a very small part of it. Environment, unquestionably, but we don't know how much, we're trying to do a lot of epidemiology on that. It's the more you understand, the more complex it gets. Interaction of things, the time in which it occurred and your role, and youth and adults and the stuff, we, polluted world, we marinate ourselves in. And there are pockets, breast cancer [and brain] seems to be real, but that's still open to research methodology. Kids that live close to transformers and get leukemia, brain tumors or whatever-have-you. These clusters, they're provocative, very few of them have led to much. ...

This interview has been condensed and edited.



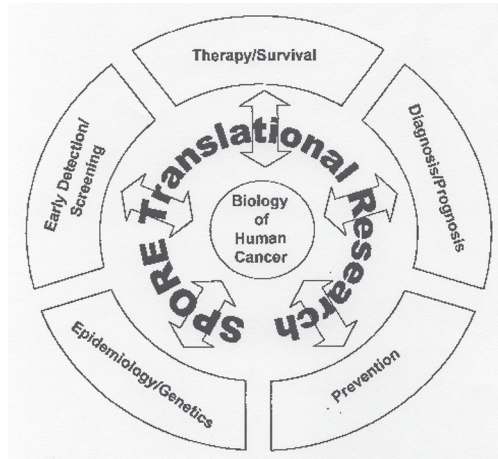
*Image featured in
"Patterns of recurrence
of glioblastoma mul-
tiforme after external
irradiation followed
by implant boost"
by David Larson,
Michael Prados, et al.,
International Journal
of Radiation Oncology
Biology Physics, 1994.*

The results of collaborative science within the BTRC soon produced new discoveries in radiation, chemotherapy, and diagnostics. The 9L rat brain tumor model was also developed and characterized, and it eventually became the most widely used animal model for brain tumor research. A completely characterized Tissue Bank was established in 1978 and collected 5000 cases over the next three decades. Wilson acknowledges that the success of the BTRC, however, was directly linked to the knowledge culture of the department itself.

Wilson's vision and ambition for clinical and basic scientific collaboration extended into an enthusiastic pursuit of futuristic technology development. After he stepped down as director of the BTRC in 1996, he subsequently became the director of the Futures Institute based in Palo Alto. In 2000 the *New Yorker* designated Wilson a 'Physical Genius' with unique sensitivities for identifying future technologies with the highest potential, highlighting his predictions that genomics, vaccines and above all technological sensors

will entirely transform healing and biomedical research in the new century. It was that kind of expansive vision which created the translational research environment of the BTRC in the early 1970s and nurtured its evolution to the point where the center was in a strong position to apply for the first SPORE awards to be made available for brain cancer in 2000. Over two years, a BTRC review panel, which included external reviewers, evaluated competitive applications for projects to be included in the SPORE application under the overall direction of Mitchel Berger who became chair in 1997. When the award was gained it funded four projects covering a wide range of research from molecular biology to clinical and population studies.

Today the largest brain tumor treatment program in the nation, the BTRC is the producer of more specialists in brain tumor biology and therapy than any other institution in North America. UCSF and the BTRC served as the lead institution and base for the North American Brain Tumor Consortium (NABTC), funded by the NCI. In January 2009, the



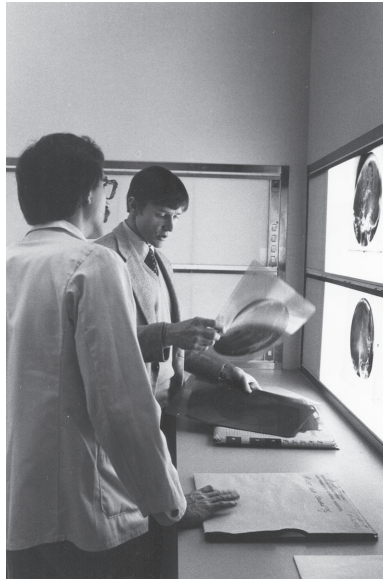
This diagram, which originated from the UCSF Brain Tumor SPORE grant from 2002-2005, demonstrates the design of SPORE research. Specialized Programs of Research Excellence (SPORE) targets organ-specific human cancers, and their projects aim to test the relevance of biological discoveries in human cancer risk, prevention, diagnosis, prognosis, treatment, and detection.

NCI mandated a merge of NABTC and NABTT to form the Adult Brain Tumor Consortium (ABTC), directed by Stuart Grossman at Johns Hopkins University and Michael Prados at UCSF.

In 2006-7 a historical investigation was completed into the use of brachytherapy for malignant glioma. This treatment uses stereotactic surgical techniques to implant radioactive material (radioisotopes in the form of beads or wires) directly into tumors or tumor resection cavities. The BTRC is recognized in the literature as having the largest single-center experience with the treatment of malignant gliomas by brachytherapy.⁴ Between 1972 and 1992, the largest series of patients enrolled in research on brachytherapy for malignant glioma worldwide was the BTRC study with 493 patients.⁵ The study of the structure of scientific interactions and professional identities during this period provided original insights into the historical emergence of a model of translational research within the BTRC that was consistent with

Wilson's original conception of bi-directional intellectual flow between bench and bedside.

A centralized group within the BTRC, the brachytherapy group, was identified as conducting this research and interacting with satellite clusters. A content analysis of historical and systematic literature reviews revealed a number of interesting points about this research. Early collaborators within the group were primarily, though not universally, identified in two major specialties: neurosurgery and radiation oncology in equal number (24% and 24%). Among later recruits to the group 28% identified themselves as neuro-oncologists, indicating the emergence of neuro-oncology as a new interdisciplinary identification amongst the brachytherapy group. One collaborator described themselves as a physicist-neurosurgeon and a one as a physicist. Twelve percent were molecular biologists and geneticists. Each of the other collaborators identified their field of specialization as neuropathologist, neurologist,



*Lawrence Pitts (right)
and a colleague
analyze film from a
patient's brain scan.*

psychiatric-neurologist, psychiatrist, computer analyst, neuro-oncology nurse, radiation therapist, and a patent attorney specializing in intellectual property law.

According to UCSF historian of medicine Dorothy Porter, from these historical data, “we discovered that the great majority of collaborators (56%) were trained as clinicians (MD), 16% were trained as basic scientists, and 12% were trained as clinician-scientists (MD/PhD). We were particularly interested in whether the collaborators had trained at the same institution, possibly with a shared mentor. We found that 51% of clinician collaborators had undertaken their medical residency at UCSF.”

The majority of the group from both clinical and basic science backgrounds left UCSF. All of the clinical translational research scientists took up high senior academic or biotechnology positions. A dominant trajectory of collaboration could be detected in recruitment as a clinical resident rising to a research and institutional

leadership position while at the same time moving from middle to first author on research publications. This indicates that the collaborative research group was functioning as a successful scientific and professional training and career development environment in translational science for investigators from clinical backgrounds. The dominant trajectory of collaboration found amongst the group also indicates that translational research supported highly successful career development both within and beyond UCSF for investigators from clinically trained backgrounds. The dominant trajectory indicates that translational research did not support career development for investigators from basic science backgrounds to the same extent.

The importance of cultivating an environment for fruitful cross-fertilization of research and investigation not only helped shape the success of the BTRC, but of the department and its training programs overall. From its humble beginnings, UCSF's Department

Department of Neurological Surgery's residents from the mid-1980s. Front row: Robert M. Levy, David S. Baskin, Brian T. Andrews, Nicholas M. Barbaro. Back row: Mitchel S. Berger, James E. Boggan, Greg Zorman, Griffith R. Harsh, Neil A. Martin.



of Neurological Surgery grew to a level of having nation-wide impact on leadership positions in the field. Reflecting on the importance of having established the first residency training program on the West Coast in neurological surgery, Philip Weinstein notes that a key indicator of the success of the department is the fact that “at least a dozen UCSF neurosurgery residency graduates are chairs of academic neurosurgery programs and departments.”⁶ Weinstein, who finished his residency at UCSF in 1967 and worked at Loma Linda and the University of Arizona before joining the UCSF faculty in 1982, named: Neil Martin at UCLA, Jim Boggan at UC Davis, and Robert Spetzler, who is director of the Barrow Neurological Institute, a private hospital and a major neurosurgery training program. Former UCSF resident Phil Gutin is chief of neurosurgery at Sloan-Kettering and was chairman of the department at UCSF for two years after Wilson. Dong Kin is chair at the University of Texas; Mark Rosenblum was resident

and faculty here and had been chair at Henry Ford in Detroit, one of the largest neurosurgical departments in world. Nicholas Barbaro, who was a resident and faculty member at UCSF, is chair at Indiana University in Indianapolis. Lawrence Pitts expressed a similar sentiment. “You can look at how many neurosurgeons who trained here as residents went to other places where they emphasized both good clinical care and research,” says Pitts. “That’s a lasting contribution. So many of the people trained here have taken the team model to other places.”

The BTRC and the formulation of “team science” through the initiatives of translational research harking back to the 1970s, in conjunction with the developing strengths in the training programs, provided a solid foundation on which to expand collaborations between neurosurgery and other disciplines and subspecialties. Indeed, as Weinstein observed, there has been an enduring combination of clinical excellence with research into a range of



In 1979, Mitchel S. Berger started his medical internship at UCSF and thereafter completed his residency in Neurological Surgery. Berger continued his career at UCSF to eventually hold positions as Professor and Chair of the Department of Neurological Surgery, the Berthold and Belle N. Guggenhome Endowed Chair, Director of the Brain Tumor Surgery Program, and Director of the Neurological Research Centers and BTRC.

areas, including spine and head injury, degenerative diseases of the spine, vascular conditions, stroke, epilepsy, Parkinson's disease and other movement disorders. "We've made significant advances in each subspecialty," said Weinstein. "The practice of pairing basic scientists with clinicians in these subspecialties was started by Dr. Wilson and has been further developed by Dr. Berger."

It is to these branches of the department that define the modern history of the department, under the leadership of the current chair, Mitchel Berger, that we now turn.

Endnotes

- 1 The Campus Bulletin, June 1970, Vol. 3, No. 3, p. 5.
- 2 Interview with Dr. Robert Weyand, August 18, 2014.
- 3 Interview with Dr. Lawrence Pitts, August 12, 2014.
- 4 Vitaz, T.W., Warnke, P.C., Gutin, P.H., 'Brachytherapy for brain tumors', *Journal of Neuro-Oncology* (2005) 73: 71-86.
- 5 Sneed, P.K., Larson, D.A., Gutin, P.H., 'Brachytherapy and hyperthermia for malignant astrocytomas', *Semin Oncol.* (1994) Apr;21(2):186-97, p. 190.
- 6 Interview with Dr. Philip Weinstein, August 20, 2014.

Out with the Old, In With the New



Demolition of old Medical School Building, 1967 with wrecking crane. From Robert L. Day Digital Image Collection, UCSF Archives and Special Collections.

Chapter Six

Branching Out: Expanding Neurosurgical Expertise

“Our neurosurgical faculty has made a commitment to bringing basic scientists to work with us — to rebuilding the department on a collaborative foundation strengthened by an underlying translational theme.”

— Mitchel S. Berger, MD

In 1994, Charles Wilson was appointed Director of Tertiary Care Services at UCSF. After 28 years, he resigned as chair of the Department of Neurological Surgery to undertake graduate study and commit a major part of his time to his new role, believing that he could serve the best interests of UCSF by acting as an intermediary between the Medical Center and outside entities ranging from health care delivery systems to health plans. He became UCSF Professor Emeritus of Neurological Surgery on January 2, 2002. After a search for a new chairman, Philip Gutin was named to chair the Department of Neurological Surgery. Shortly afterward, having been offered the position of Chief of the Neurosurgical Service at Memorial Sloan Kettering-Cancer Center in New York, Gutin left UCSF. Wilson resumed the chairship while another search was undertaken and in April 1997, Mitchel S. Berger was recruited from the University of Washington, Seattle, to return to UCSF to assume the position as Department Chair and the BTRC’s Director.



Mitchel Berger, MD

The new millennium brought new possibilities for advancing clinical and research services. New techniques such as gene sequencing and molecular biological methods, along with transgenic animal modeling, created fresh opportunities for bench-to-bedside translational research. Under Berger's guidance, the Department expanded translational research partnerships and designated different neurosurgical research interests that are amenable to the translational approach.

When Berger chose to return to the place of his residency to

take up the chairship of UCSF's Department of Neurological Surgery he was driven by the desire to restore this outstanding leader in academic medicine to the root of its reputation in research-driven, innovative therapeutics.

UCSF's leadership in academic neurosurgery was derived from the philosophy integrating theoretical knowledge with clinical practice that had been nurtured and governed the Department since its foundation under Naffziger and vigorously promoted and supported by Charles Wilson. As a result it came to dominate the Bay Area in referrals for specialist

neurosurgical procedures. Changes in the structural funding of health care delivery with the rise of managed care undermined UCSF's established role in the health market as a specialist clinical facility.

The impact of these changes upon the Department of Neurological Surgery was gradual erosion of clinical specialization and, as a result, translational research investigation. Clinical practice became increasingly generalized with practitioners undertaking a diverse range of procedures including less complex and more superficial interventions. For example, surgeons who had specialized in deep brain stimulation were undertaking more common procedures such as the surgical placement of shunts.

As clinical practice had become increasingly generalized within the department, basic scientific research within and beyond

the department had become increasingly individualized as the result of the dominant NIH R01 primary investigator funding model. Within neurosurgery specifically, team science that had uniquely characterized its pioneering research profile from the foundation of the BTRC in 1972 was being replaced by research silos directed by the interests of primary investigators and funding mechanisms.

Berger's mission on arriving at UCSF was to move away from generalist practice and individualized research silos. He strategically restructured fund accumulation and income distribution to facilitate the recruitment of subspecialists who would integrate their clinical practice with translational research investigation and original discovery, in basic scientific knowledge and/or technological innovation. In addition, Berger

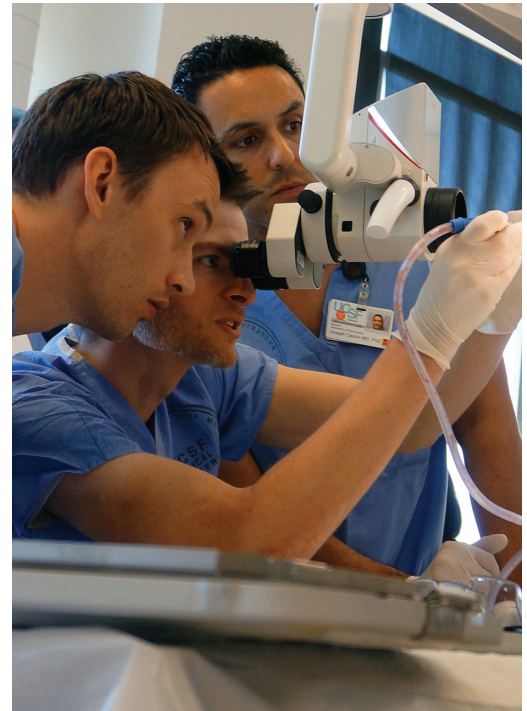


*Faculty in the
Department of
Neurological Surgery*

Residents Jonathan Breshears, Jason Davies, and Joseph Osorio perform surgical simulations on cadavers in a state-of-the-art surgical anatomy lab

fostered collaboration between subspecialist practitioner/clinical researchers with basic scientific investigators in the molecular life sciences. The proliferation of cross departmental Centers and the unique creation of 'Research Funding Organizations' at UCSF modeled on the original BTRC were created as a result of UCSF's exploratory intellectual culture that had grown since the early 1970s and led by a highly interdisciplinary Nobel Prize winner and Chancellor, Michael Bishop. This culture of intellectual liberalism melted disciplinary boundaries to favor the pursuit of original and ground-breaking analytical questions.

Berger perceived that subspecialist recruitment was the way to harness the culture of interdisciplinary research and rebuild team-based research exploration within the department that would rejuvenate its recruitment capacity. In 1997



there were fewer than 12 full-time faculty members in the department. Today there are 60 full-time basic and clinical science faculty members, 21 of whom have been hired since 2008. Support staff has also increased by 60% in the last decade, with 148 academic and clinical employees.

Russell Pieper, PhD, Principal Investigator and Director of Basic Science at the Brain Tumor Research Center



A Triple Threat

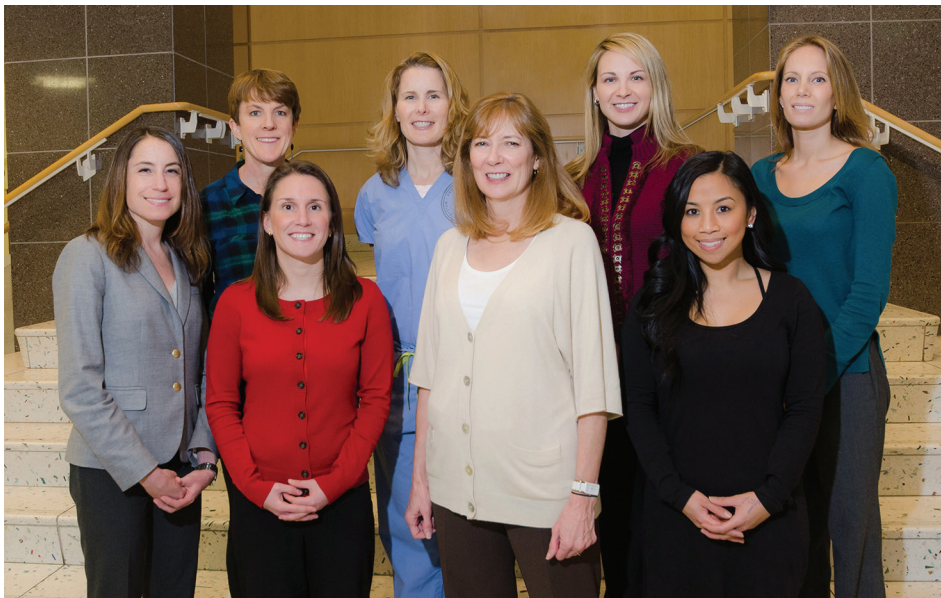
As pioneering and prestigious as the clinical and scientific collaborations have been for brain tumor research, this is one of many areas of specialization for which UCSF is now recognized for its leadership and innovation. Under Berger's leadership, the Department of Neurological Surgery has become a prime representation of UCSF's triple mission: to advance clinical care, research, and education.

Today UCSF is ranked fourth in the nation for neurology and neurosurgery services by *U.S. News & World Report* – and first on the West Coast overall and first in the nation among public institutions. It has maintained a position as one of the top five programs in the nation since 2007. The Department's average Press-Ganey Scores, reflecting patients' likelihood to recommend services,

are above 90% in cranial and spinal neurosurgery. The average score for the Neuro-Oncology Service is 97%. In 2007, UCSF Medical Center introduced the Pinnacle Award for the single best outpatient care service and the Neuro-Oncology Service has received the award every year since that time.

On congratulating the Neuro-Oncology team for their seventh consecutive win in 2013, Dr. Berger spoke of the philosophy that has given the Department one of the best reputations in patient care, saying, "I believe in treating every single one of my patients like they are a member of my family, and I believe it's that level of care that we all need to exhibit every day in order to continue being the best."

As the leading tertiary referral center for neurosurgery in the Bay Area, UCSF began to expand its clinics to surrounding



*Neurosurgery nurses
and nurse practitioners*

*Operating room
team members*



communities in 2012 in order to provide extended services to Bay Area residents and physicians. Today the Department has formed partnerships with Marin General Hospital, Queen of the Valley Medical Center in Napa Valley, and Good Samaritan Hospital in San Jose so that patients may see specialists closer to home and so that there can be greater continuity of care between specialists and referring physicians. The Marin

group is led by Tarun Arora MD, Keith B. Quattrocchi MD, PhD, and Rishi Wadhwa MD; the Napa Valley group is led by Soren Singel MD; and the pediatric clinic in San Jose is led by Corey Raffel MD, PhD.

In academic research, no other neurological surgery program receives more extramural NIH funding. For 14 consecutive years, since 2000, the UCSF Neurological Surgery Department has topped

*Operating room
team members*



*Clinic staff*

the nation in funding from the NIH, reflecting the caliber of research being performed. From resident National Research Service Awards to team science Program Project Grants, research funding totals over \$20 million per year. Among academic neurosurgery programs, UCSF also ranks first in the nation in overall research publication productivity (mean Scopus h-Index: 32.15; Σ h-Index: 625).

The Department offers a variety of rich educational programs tailored for individuals ranging from medical students to nurses to visiting scholars from 30 countries around the world. But it is perhaps most revered for its rigorous residency program. What began as a three years of training in 1934 is now a seven-year immersion into every subspecialty of neurosurgery, including one year devoted to research. Over

*Academic staff*

National Rankings

#1 Neurological Surgery Program
on the West Coast and #4 in the Nation

US News & World Report

#1 Research Funding for Neurological
Surgery Programs (2000-2014)

National Institutes of Health

#1 Research Publication Productivity

Journal of Neurosurgery*

#1 Neurological Surgery
Residency Program in the Nation

Doximity and
US News & World Report

* Khan NR, Thompson CJ, Taylor DR, et al. An analysis of publication productivity for 1225 academic neurosurgeons and 99 departments in the United States. Journal of Neurosurgery 2014; 120:746-755.

200 candidates applied to fill three positions in 2014. That same year the program was named best residency program for neurosurgery in the nation by Doximity and *US News & World Report*. It is the mission of the Department to train future academic neurosurgeons who will continue to advance the field; since 2000, 87% of graduates

have gone on to academic positions or fellowships.

The following sections provide glimpses into the evolution and expansion of neurological surgery to subspecialties. While not by any means exhaustive, we aimed capture some of the innovative work that has been achieved over the years. What has emerged is a picture of an evolving organism

with a complex structure, not unlike the brain itself. It continues to form new pathways, built together by a remarkable group of faculty members in collaboration with the many nurses, physicians' assistants, staff members, and collaborators that support them in their mission to create the best neurosurgery program in the world.

SPOTLIGHT

Amazing changes in techniques and technology have changed the profile of neurosurgery throughout the last hundred years, not only at the University of California but world-wide. It is fitting, therefore, to turn our attention to the reflections of one of our most esteemed surgeons who has seen more change than most, Dr. Robert Weyand.

For 91-year-old Robert Weyand, whom UCSF neurosurgeon Grant Gauger described as "the dean of East Bay neurosurgeons," the biggest change over his career has been "so many incredible improvements in our ability to diagnose neurological conditions." In a discussion we had with him in August, 2014, he cited as examples the use of X-rays, contrast media, CT scans, and MRI. "We used to put air in ventricles," he said. Another key area of progress has been in surgical techniques, including "giant advances in anesthesia," endoscopic surgery, and the use of video cameras as an operating tool.

Weyand sees UCSF as "clearly in the top five in the United States in training practitioners," and feels the school has done "an incredible job in educating both health care providers and the broader public."

Reflecting on the interactions between researchers and clinicians, Weyand believes that "the concept of the scientific method is and remains crucial." This method is needed as a way to mitigate

and "filter out" misinformation. The scientific method and the use of statistics have been essential to advances in neurosurgery; they are the best ways to ground these advances in a consistent methodology and to produce findings that others can either replicate or challenge.

For Weyand, Wilson was "the premier guy – an incredible technician." When Wilson first got to UCSF, "I thought he'd have some trouble. But he reached out to people in different functions and specialties very effectively." Weyand's own career has reflected a blend of clinical and research work. He worked for several decades at the county hospital. He focused on pediatric neurosurgery

for 10 years, and has mentored many nurses and doctors throughout his career. Weyand has been very involved in professional societies, which play an important role in education of doctors and others. Another dimension of Weyand's career has been on the political and advocacy side. He and Byron Pevehouse formed a political ac-

At UCSF, Howard Naffziger was "a pioneer in decompression for exothalamus." "I did surgery with Naffziger," Weyand said. "He was a pioneer in diagnosis and was deeply interested in the person we were treating, not just the condition. I think we have held on to that legacy quite well."

tion group that successfully lobbied for legislation on malpractice for neurosurgeons in California. "The trial lawyers are still trying to overturn it," he said.

Neurospinal Disorders

Faculty

Christopher Ames, MD
 Praveen Mummaneni, MD
 Dean Chou, MD
 Philip Weinstein, MD
 Aaron Clark, MD, PhD

According to Philip Weinstein, MD, after Wilson stopped performing neurosurgical procedures it took five or six surgeons in each subspecialty to take over his practice. Weinstein, who graduated from the UCSF neurosurgical residency program in 1966, took over Wilson's practice for spinal conditions and developed an interest in spinal stenosis and deformity. Together with Wilson and George Ehni, he edited the first book in the U.S. medical literature on lumbar spinal stenosis, published in 1977.

Although now considered one of the most common neurospinal disorders, lumbar spinal stenosis was not recognized and treated until 1960. Symptomatic lumbar spinal stenosis is characterized by neurogenic claudication and/or lumbar or sacral radiculopathy, neither of which were well understood prior to the 1960s. When lumbar spinal stenosis became more widely recognized, Weinstein was a proponent of early imaging and surgery to prevent permanent neurological sequelae of chronic nerve root entrapment. From the early 1990s to 2000s, surgery for stenosis was primarily decompression by wide laminectomy or an intralaminar

approach. While these types of surgeries are still performed, minimally invasive options have become available, such as the lamino-foraminotomy procedure.

Today the UCSF Spine Center has five full-time neurosurgeons, collaborating with many other specialists, and offers a complete spectrum of care from nonoperative techniques to full spinal reconstruction. Spinal trauma is concentrated within the Brain and Spinal Injury Center. The neurosurgeons who specialize in spinal procedures have further subspecialized and focus their practices in the key areas of spinal deformity, spinal tumors, and minimally invasive spine surgery. Together they perform over 1000 complex spinal procedures per year.

Spinal Deformity

While relief for patients with stenosis was improving in the later half of the 20th century, not much could be done for patients with complicated deformity cases. David Bradford, MD, professor and chair emeritus of the Department of Orthopaedic Surgery, pioneered some of the early deformity surgeries, but they were very invasive – some patients would have their entire blood volume transfused during surgery – and complication rates were high. As acquired spinal deformity usually becomes symptomatic in older patients, it was also risky to perform these types of surgeries in that patient population.



Neurosurgeon Christopher Ames, MD and orthopaedic surgeon Vedat Deviren, MD operate together on a patient with severe spinal deformity

Most patients undergoing spine surgery were given a halo ring – a device pinned to the skull to stabilize the cervical spine – that they would need to wear for four to five months. While offering relief for some patients, they were also dangerous. If a patient fell over, for example, the pins holding the halo in place could be pushed into the skull. The halo was phased out beginning in the early 2000s and has only been offered in rare cases since 2010.

Before 2001 it was rare to put instrumentation into a patient to stabilize the spine because the available instrumentation was weak and had high failure rates. Steel rods, for instance, could cause infection and titanium rods would sometimes crack. Today, the majority of deformity procedures are done with complex instrumentation that is stronger and more versatile. The development of cobalt chrome rods was an innovation that overcame the previous shortcomings of the steel and titanium rods. As with other neurosurgical subspecialties, improvements in neuroimaging significantly changed the types of surgeries that could be

performed. Computer-assisted neuronavigation in the operating room suddenly allowed screws to be placed into tighter spaces with minimal danger of hitting blood vessels or spinal cord.

In 2002, Christopher Ames, MD, joined the Department after completing a spine fellowship at Barrow Neurological Institute. He and orthopaedic surgeon Vedat Deviren MD developed another key innovation for deformity surgery: the two-surgeon approach. During these procedures a neurosurgeon and orthopaedic surgeon operate simultaneously, dramatically reducing operating times and blood loss. This was especially a boon to older patients who could not tolerate 12-hour procedures that were the norm for many deformity surgeries. The patient also benefits from the individual expertise of each specialist. After the UCSF team published their outcomes, neurosurgeons at other academic institutions began to follow suit and operate alongside their orthopaedic colleagues.

A greater collaboration between orthopaedic and neurosurgeons in general is another important

The multidisciplinary team at the UCSF Spine Center



development in spine surgery. Historically the two fields have been competitive, but in the first decade of the 21st century a shift in the culture made it possible for these two specialties not only to be collegial but to collaborate. Today, orthopaedic surgeons and neurosurgeons attend many of the same conferences and co-publish clinical research papers, greatly enhancing both fields.

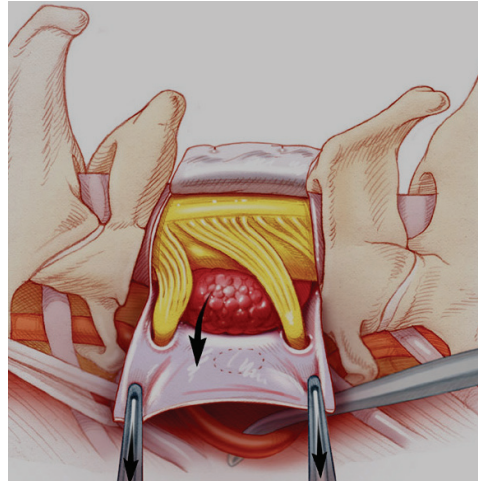
By 2014, the neurospinal disorders group was performing nearly 200 surgeries for deformity each year, giving the department one of the busiest spinal deformity practices in the nation. This vast experience with deformity operations, and an increasing need for these procedures by a population of aging Americans who expect to be active in their later years, led to the establishment of the California Deformity Institute at UCSF. Co-directed

by Ames and Deviren, the goal of this new institute is to provide multidisciplinary specialty care that incorporates the current best evidence in medical decision-making.

In a landmark paper published in *Neurosurgery* in 2012, Ames and his colleagues showed that sagittal alignment of the cervical spine is correlated with better health-related quality-of-life scores after cervical spine fusion surgery. This study was the first to show that cervical alignment is linked to outcomes in the same way that lumbar sagittal balance is linked to outcomes after lumbar fusion surgery. As a result, patients treated at the California Deformity Institute now undergo standing preoperative and postoperative cervical radiographs and 3-foot standing films to allow the spine surgery team to plan ideal postoperative cervical alignment.

Spinal Tumors

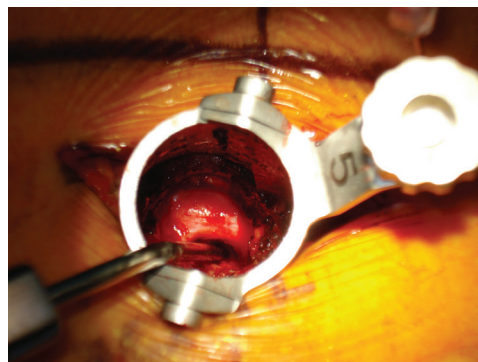
Intraspinal tumors of the anterior midline cervical and cervical thoracic region have historically posed a significant surgical challenge and high surgical risk because of the severe neurological damage that can result when manipulating the spinal cord. In 2005, Ames developed a surgical technique to operate on these tumors, called a lateral transpedicular approach, which he described as “skull base surgery for the spine.” It involves radical bone resection, effectively removing the entire spine on one side to provide direct access to the tumor while avoiding manipulation of neural elements. He also began specializing in en bloc resection for spinal tumors, which involved creating wide margins to avoid violating the tumor and causing the spread tumor cells. At that time UCSF was the only institution on the West Coast routinely performing the kind of radical tumor resections for primary spinal tumors advocated by Ames.



The lateral transpedicular approach with corpectomy essentially “delivers” tumor out from underneath the spinal cord without any spinal cord retraction

Minimally Invasive Spine Surgery

While aggressive resections were improving outcomes for some tumor patients, on the other side of the country another revolution in spine surgery that focused on smaller openings was coming into its own. Praveen Mummaneni, MD, a resident in the Department of Neurological Surgery from 1997 to 2001, completed fellowship training in minimally invasive



Minimally invasive transpedicular discectomy of the thoracic spine is performed through a tube just 26 mm in diameter

spine surgery at Northwestern University under the tutelage of Lawrence Lenke, MD, and at Emory University School of Medicine under Hayden Rodts, MD. First developed circa 2002 by Steve Ondra, MD and Christopher Shaffrey, MD, minimally invasive spine surgery allowed what was traditionally done in wide open laminectomies to be done through tubes as small as 26 mm in diameter. Advantages for patients included less blood loss, shorter hospital stays, shorter recovery times, lower risk of infection, and less pain. Mummaneni brought those techniques to UCSF when he returned to join the faculty in 2006, and the Department is now a nationwide leader in furthering this field. Mummaneni was a staunch advocate of pushing the boundaries for what could be achieved through a narrow tube, lecturing at international meetings on six continents about the merits of minimally invasive surgery. He is now internationally recognized for his work on cervical kyphosis and minimally invasive approaches to spinal deformity surgery and spinal tumors.

Dean Chou, MD, who was a neurosurgery resident at the Johns Hopkins Hospital and underwent fellowship training in spine surgery at Barrow Neurological Institute prior to becoming a faculty member in 2005, has also made several contributions to advancing minimally invasive techniques for complex spinal conditions. Over his career Chou developed a special interest in using

minimally invasive procedures to treat complex problems of the thoracic spine, and he and former resident Daniel Lu, MD were the first to describe a mini-open transpedicular corpectomy with expandable cage reconstruction to treat thoracolumbar pathology. This procedure allowed decompression of the spinal cord through a single posterior incision instead of the standard approach through the chest or abdomen, and the circumferential decompression resulted in improved neurological recovery.

Today, minimally invasive procedures are performed at UCSF for conditions ranging from degenerative diseases to spinal tumors and spanning the cervical, thoracic and lumbar spine. Even vertebral column resection for severe rigid deformity can be done minimally invasively. As Chou noted in a 2012 interview, “Major operations for deformity were the last frontier for minimally invasive surgery.”

In 2015, former resident Aaron Clark, MD, PhD returned to UCSF after performing a fellowship in minimally invasive spine surgery at the Semmes-Murphey Neurologic and Spine Institute in Memphis, Tennessee under the mentorship of Kevin Foley, MD. Clark brings minimally invasive techniques to the outpatient setting – performing procedures for herniated discs and stenosis that allow patients to return home the same day.

Neurospinal Disorders Research

As the neurospinal disorders group continued to develop new surgical techniques, they systematically and analytically reviewed patient outcomes to implement the best evidence-based practices. All of the faculty are involved with multicenter, international studies and research organizations like the Scoliosis Research Society and the International Spinal Deformity Study Group.

Mummaneni served as a principal investigator on a multicenter, prospective, randomized study evaluating the Prestige artificial cervical disc against anterior cervical discectomy and fusion. In 2014, the group published seven-year outcomes (the fourth set of outcomes to be published from the study), which is one of the longest follow-ups for this type of investigation. Mummaneni and Weinstein had both been proponents of using technologies that preserve cervical motion over fusion. The seven-year outcomes of the Prestige trial showed that the artificial disc was a better solution for preserving motion at the operated level and offered increased biomechanical stability and global neck mobility over fusion. As recently as the year 2000, “long-term” follow-up in clinical studies was often measured in months rather than years, and studies were often performed without well-defined outcome measures. UCSF neurosurgeons

have been at the forefront of improving study design – such as that of the Prestige trial – to more accurately evaluate efficacy of both new and established procedures.

Research into spinal reconstruction after radiation therapy earned Ames the prestigious 2005 International Society for Study of the Lumbar Spine (ISSLS) research award. In 2013 he was honored with the Whitecloud Award for best clinical paper at the 20th Annual Meeting on Advanced Spine Techniques, and he served as the UCSF site PI for the Scoli Risk 1 Trial – the first prospective, international study of rates of neurological injury following severe deformity correction and complex osteotomy. Early published results of the study earned the Scoli Risk 1 Trial team the Russell S. Hibbs Clinical Award from the Scoliosis Research Society. Ames also directs a laboratory that studies spinal biomechanics in cadavers.

Brain and Spinal Injury Center

Faculty

Geoffrey Manley, MD, PhD
 Michael Beattie, PhD
 Sanjay Dhall, MD
 Michael Huang, MD
 Phiroz Tarapore, MD
 Jacqueline C. Bresnahan, PhD
 Adam R. Ferguson, PhD
 Linda J. Noble-Haeusslein, PhD
 Susanna Rosi, PhD

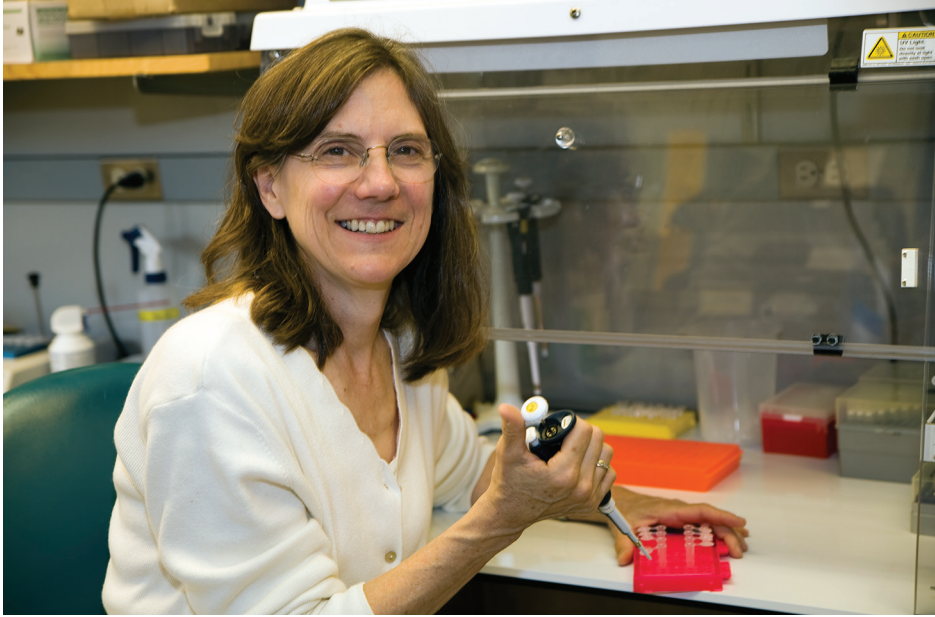
After completing residency in the Department of Neurological Surgery in 1969, Lawrence Pitts, MD joined the faculty. In 1976, he was awarded the Van Wagenen Fellowship from the American Association of Neurological Surgeons and spent eight months at the Institute of Neurological Sciences in Glasgow, Scotland where he worked with Sir Graham Teasdale and Bryan Jennett – authors of the 1974 Glasgow Coma Scale, which would become the standard for assessing patients with traumatic brain injury (TBI) for the next 40 years.

Upon returning to San Francisco, Dr. Pitts became chief of neurosurgery at San Francisco General Hospital (SFGH), and remained so for 17 years. During this time he published many studies on neurotrauma and was actively involved in professional organizations that established guidelines for treating brain and spinal cord injuries. He served as chairman of the Joint Section on Neurotrauma of the AANS and the Congress of Neurological Surgeons, and served on its

executive committee for many years. He also served on the American College of Surgeons Committee on Trauma. In 1994, he was elected chairman of the American Brain Injury Consortium, and was actively involved in clinical trials research of head injury. Throughout his career he argued for the release of clinical trials data by sponsoring companies, which was often withheld if the trials were negative. He asserted that proper dissemination of data following the completion of trials was essential for improving the design and execution of future trials. Dr. Pitts was also interested in academics, serving on various UC Academic Senate committees. He became the University of California's provost and executive vice president-academic affairs in 2010. The provost is the highest-ranking academic officer at UC and is responsible for academic affairs system-wide.

Historically there had been collaboration between researchers and clinicians interested in neurotrauma, resulting from the culture of team science established by Wilson. Pitts recalls, "I would be working on a problem in neurotrauma or head injury and someone from the research side would hear and come to learn more and perhaps begin working with me."

There had also been cross-pollination between subspecialties, perhaps exemplified by the work of John Fike, PhD, recently retired after 33 years at UCSF as Professor of Neurological Surgery, Radiation Oncology and Radiology. In 1982, Fike became a



*Linda Noble, PhD,
Principal Investigator
at the UCSF Brain and
Spinal Injury Center*

principal investigator at the BTRC, when investigators were refining radiation therapy and defining new applications for its use. Fike's laboratory investigated the cellular basis of radiation injury using both in vitro and in vivo models. His work reflected a growing interest in understanding the effects of radiation not just on the targeted cells but on normal tissues. His work on radiation injury to the brain became aligned with other researchers investigating cellular mechanisms of CNS injury, and his laboratory eventually moved to the Brain and Spinal Injury Center.

Reflecting on some of the major developments in this area of research, Fike said "One of the biggest changes in radiation biology since I started at UCSF is a much greater focus on what happens to normal cells that are exposed to radiation in the course of treatment. It used to be that if a person survived the surgery, radiation, and chemotherapy, we felt we had done our job. Over the last few decades there has

been much more interest in the impact on the functionality of non-cancerous cells that survive irradiation. This is a huge change in the criteria for success. When I first got to UCSF I was the only person who was really looking at the 'good' cells. Today we have a large database of children who were irradiated and/or operated on and who have had significant functional and behavioral issues later on. We've also seen growing interest in what I would call the biological dimensions of the ways in which the brain and tumors respond to radiation. The work to understand how genes operate is getting steadily more valuable in this regard."

Linda Noble-Haeusslein, PhD was also interested in the problem of central nervous system injury and her laboratory focused on the neurobiology of traumatic injury. Joining the faculty at UCSF in the Department of Neurology in 1985 and the Department of Neurological Surgery in 1990, she was also director of the Program

San Francisco General Hospital and UCSF have had a long and productive partnership in providing high-level neurotrauma care in the Bay Area



for Neurotrauma Research and a principal investigator in the Center for Neurologic Injury and Repair (CNIR) who showed that cellular responses to blood-brain barrier disruption do not reflect irreversible injury but may in fact represent a state of heightened neuroprotection. The hypothesis was based on the innovative observation that transient barrier breakdown, in the absence of trauma, results in the widespread induction of the stress protein HSP32 (heme oxygenase-1), and that this occurs in the absence of irreversible neuronal injury. Developing experimental models of traumatic brain and spinal cord injury in the rodent, her studies focused on the role of the blood-brain and blood-spinal cord barriers in early pathogenesis after traumatic injury, the acute and chronic influences of inflammation on both injury and repair mechanisms, and the identification of those cellular defense mechanisms intrinsic to the brain and spinal cord that protect against secondary

injury and may be essential for limiting the extent of cell injury.

To focus on clinically relevant problems, the basic scientists initiated more collaborations with the physicians working at SFGH. The long and productive partnership between UCSF and SFGH has been essential for the growth of the Department's neurotrauma program. The roots of this relationship go back to the 1906 earthquake, when the trauma center that we know today began to take shape on the SFGH campus. In 1991 it was designated a Level 1 trauma center – a tertiary care facility capable of providing total care for every aspect of injury. In 2001, SFGH established a formalized Traumatic Brain Injury Program under then Chief of Neurosurgery Martin Holland, MD, which was focused on improving the efficiency of the care system for trauma patients. Holland recognized that the greatest impact on outcome came not from surgical technique but from timely admittance and postoperative care. The TBI Program aimed to streamline the



Geoff Manley, MD, PhD, Co-Director of the Brain and Spinal Injury Center speaks with healthcare providers at SFGH

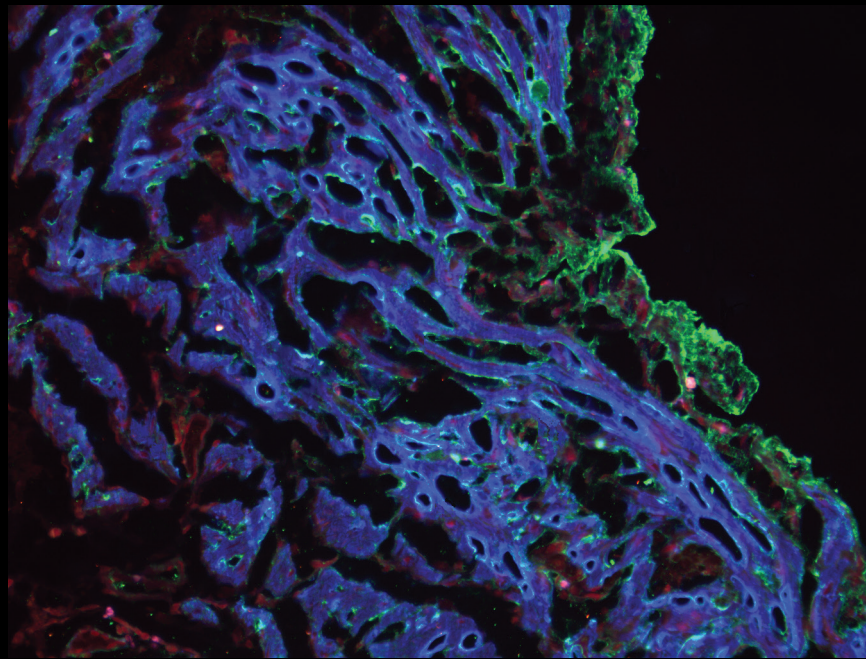
many phases of care from triage to rehabilitation. Holland had joined the Department in 1997 as an assistant clinical professor of neurosurgery along with David McKalip, MD, and together they served as co-directors of the CNS injury program at SFGH. McKalip also worked in the lab to develop strategies to promote regeneration in the CNS through gene transfer technology. In 2004, Holland left UCSF to join the Navy and contribute to advancing neurocritical care for injured servicemen and women. During this time Grant Gauger, MD was also instrumental in steering the program at SFGH, serving as acting chief of the neurological surgery service there for nearly a decade from 1993-2001.

SFGH has also been an important training ground for UCSF neurosurgery residents. In 1995, Geoffrey Manley MD, PhD arrived at UCSF as a neurosurgery resident and his first rotation was at SFGH learning from Lawrence Pitts. Manley quickly developed a sustained interest in neurotrauma, and in 1997 was awarded first

place in the Resident Research Competition of the American College of Surgeons Committee on Trauma. In 1998, he became a resident member of the Executive Committee of the Neurotrauma and Critical Care Section of the AANS/CNS to offer a resident's perspective. While completing residency, Manley performed a postdoctoral fellowship at the UCSF Cardiovascular Research Institute in molecular biophysics. Manley succeeded Holland as chief of neurosurgery at SFGH and began a new era of translational research in brain and spinal cord injury. He credits Pitts for mentoring him, saying "Larry built the program, and I've tried to expand on that foundation." In 2011, under Manley, SFGH became the first hospital to gain Joint Commission certification for TBI, which recognized the clinical excellence and research leadership at SFGH in the field of TBI.

While many of the translational research collaborations in the Department came from pairing clinicians with basic scientists, the Department was also rich

The laboratory of Linda Noble, PhD, has shown that the drug MMP-9 can improve bladder function after moderately severe spinal cord injury. This image shows urinary bladder tissue of a spinal cord-injured mouse 6 weeks after injury. Collagen III is interspersed in the muscle layer after injury, suggesting that scarring has occurred.



in physician-scientists. From the outset of his career, all of Manley's research had direct clinical relevance and he tried to both understand the molecular causes of brain and spinal cord injury and improve clinical care for neurotrauma patients. In the early 2000s, he determined that direct monitoring of brain tissue oxygenation and ischemic metabolites could better detect episodes of cerebral ischemia in patients with brain injury than the current clinical monitoring techniques. Manley also investigated brain oxygenation during hemorrhagic shock, metabolic monitoring of severely injured patients during resuscitation and critical care, and the role of aquaporin water channels in cerebral water transport.

In 2002, Manley and Noble-Haeusslein, together with neurologist Claude Hemphill III,

MD, became directors of the new Brain and Spinal Injury Center (BASIC), based at SFGH, which effectively replaced the CNIR. The mission of the new center was to bring together a multidisciplinary group of clinicians and researchers to work on brain and spinal cord injury the same way it had been done for brain tumors.

The same year, Noble-Haeusslein and her colleagues discovered that mice with moderate spinal cord injuries could significantly improve their functional recovery if they were given the drug GM6001. The drug is an inhibitor of matrix metalloproteinase-9 (MMP-9), which facilitates leukocyte infiltration past the blood-spinal cord barrier during the acute phase of injury and incites an inflammatory cascade that worsens the severity of the injury. Today the Noble-Haeusslein lab continues to investigate GM6001 and has shown that



*Jacqueline Bresnahan
PhD and Michael
Beattie PhD,
Co-Director of the
Brain and Spinal
Injury Center*

the drug's therapeutic window can be as long as 8 hours and is most effective with moderate spinal cord injuries. Much of this work has been funded by the U.S. Department of Defense and is providing more evidence for the clinical need to quickly dampen the secondary effects of blood-brain barrier disruption in the spinal cord. The Noble-Haeusslein lab also uses rodent models of TBI to study how injury to a developing brain can lead to social deficits later in life.

In 2006, the husband-wife team of Michael Beattie, PhD and Jacqueline Bresnahan, PhD was recruited to BASIC from Ohio State University, and Beattie became a co-director of the center. Their laboratory was well known for developing preclinical models to study recovery of function after spinal cord injury, and for studies of the biology of neural injury and repair. At BASIC they have conducted several cutting-edge analyses of the interrelationship of

post-injury inflammatory events and excitotoxic cell death, the roles of oligodendrocyte death and replacement in recovery after injury, and the development of stem and progenitor cell transplantation strategies for promoting recovery after spinal cord injury. They have also been funded by the U.S. Department of Defense to develop preclinical models of combined head and spinal cord injury, which presents the unique clinical problem of which injury to treat first.

As BASIC continued to bridge gaps between clinicians and basic scientists working on specific problems, Manley began zeroing in on a much larger issue affecting the field. TBI is heterogeneous in cause, severity, pathology and clinical course, and a lack of validated outcome measures and data collection standards have greatly hindered the development of new treatments. "For diseases like cancer, modern classification systems are a

mixture of anatomy, physiology, metabolism, immunology, and genetics,” he said in a 2008 interview. “For TBI we have mild, moderate, and severe. Within those categories there are no standardized definitions across treatment centers and neuroimaging is only adjunctive.”

Despite decades of research and over two dozen clinical trials, there had been no new effective therapeutic developments for patients with TBI, partly because patients with vastly different injuries have been enrolled into the same treatment groups. To drive the development of a new TBI classification system, Manley began leading national and international efforts to create a modern knowledge warehouse that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers of TBI. As demonstrated in other diseases, a more precise classification of TBI could revolutionize diagnosis, direct patient-specific treatment, and improve outcome.

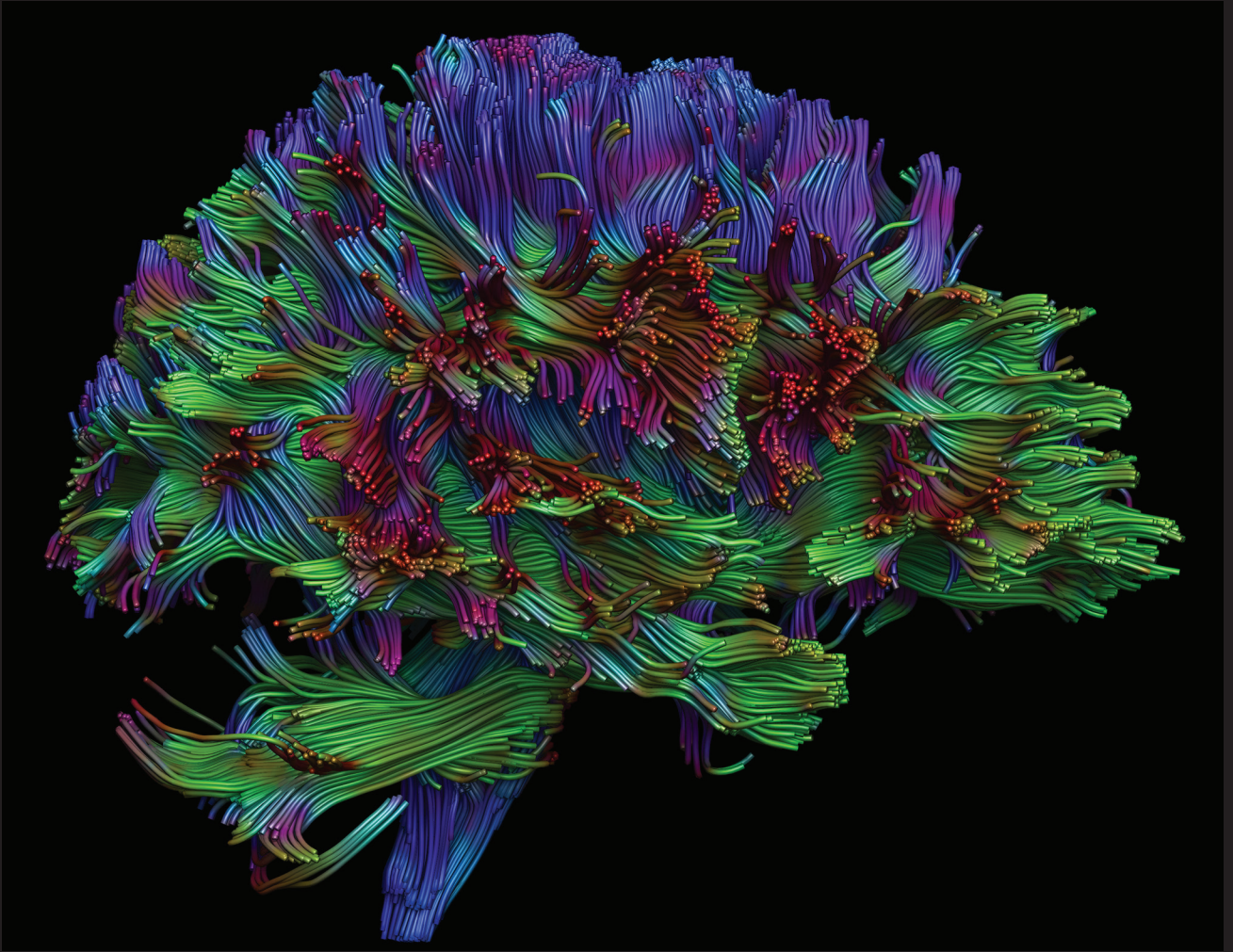
As Manley and his colleagues began advocating for a national overhaul of TBI clinical standards, an increasing number of soldiers began returning from war in Iraq and Afghanistan with traumatic brain injuries caused by roadside bombs – so many that it has been called the signature wound of these wars. As a result, the federal government began heavily investing in new research for treating TBI.

In 2009, investigators at BASIC – led by Manley and Pratik Mukherjee MD, PhD, a professor of

radiology and biomedical imaging – joined a working group that collaborated with neuroscientists at the National Institutes of Health (NIH) and the U.S. Department of Defense to develop the Common Data Elements (CDE) for Traumatic Brain Injury: new standards for reporting and defining brain injuries across studies to transform care for patients. Once developed, a \$4.1 million Grand Opportunity Grant, part of the American Recovery and Reinvestment Act, funded a prospective, longitudinal study called TRACK-TBI (Transforming Research and Clinical Knowledge in Traumatic Brain Injury) to test and refine the CDE. UCSF served as the coordinating center for the study, which was performed at four sites: SFGH, University of Pittsburgh Medical Center, University Medical Center Brackenridge, and the Mount Sinai Rehabilitation Center.

The study confirmed the feasibility of collecting robust data and establishing data repositories for clinical informatics, biospecimens, neuroimaging, and neurocognitive outcome assessments. These data were the first to be entered into the new Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system – a national informatics platform developed to share data across the entire TBI research field and to facilitate collaboration between laboratories, as well as interconnectivity with other informatics platforms.

The shift in traumatic brain injury research and classification



also began taking place abroad and the first cooperative international group to perform prospective studies of head injury was established in October 2011. Led in the United States by Manley, the International Traumatic Brain Injury Research (InTBIR) Initiative brought together the NIH, the Canadian Institute of Health Research, and the European Commission. In 2013, the NIH granted \$18.8 million

to a team of U.S. researchers at more than 20 institutions who were participating in the InTBIR Initiative. The award, now in its second year, is administered through UCSF and is one of the largest international research collaborations ever coordinated by funding agencies. At UCSF the award funds a continuation and expansion of TRACK-TBI,

Image: Diffusion tensor imaging of a mild traumatic brain injury

accessible “TBI information commons” to integrate clinical imaging, proteomic, genomic, and outcome biomarkers from subjects across the age and injury spectra.

In 2014, BASIC was one of the recipients of a \$17 million, five-year award from the U.S. Department of Defense to fund a public-private partnership specifically to improve clinical trials for TBI. The new research initiative, called the TBI Endpoints Development (TED) Award, brings together leading academic clinician-scientists, the FDA, biotechnology and imaging technology leaders, patient advocacy organizations, and philanthropies. The goal is to collect a broad range of long-term data from existing studies that have been performed in both the academic and private sector, and integrate these into a common database. The information gained from TED will be combined with that gained from the TRACK-TBI study, allowing the researchers to apply landscape analysis to identify effective measures of brain injury and recovery. As Lawrence Pitts highlighted during his career, the sharing of data from industry studies is crucial to the improvement of future research.

As TBI became more visible in the media when it became a signature of the wars in Iraq and Afghanistan, concussion was also brought into the spotlight

when studies of athletes suffering repetitive head injury tied brain injury to some types of psychological disorders and even neurodegenerative disorders like dementia. In response to this information, the National Football League created a Head, Neck and Spine Committee made up of leading physicians to consult on issues related to concussion in football. Chair Mitchel Berger was named a member of the committee, focusing on retired players issues and studies of repetitive head injury. UCSF also began outreach to school athletic programs about safe play guidelines and created a dedicated concussion clinic where patients are seen by experts from many fields – including sports medicine, physical rehabilitation, neuropsychology, neuroradiology, neurology, and neurosurgery – in one clinic visit.

While Manley and his collaborators worked to re-invent guidelines for classifying traumatic brain injury, BASIC principal investigator and bioinformatics expert Adam Ferguson PhD began to do the same for preclinical models of spinal cord injury. The outcome measures being reported in clinical literature are generally very different from the outcome measures reported in the preclinical literature. This disconnect in reported outcomes is a hurdle to translating laboratory findings into useful clinical

therapies and has prompted Ferguson and his colleagues to develop a preclinical set of CDE that mirror the clinical CDE for spinal cord injury that are currently under development by the NIH. Ferguson expects that in applying multivariate analysis to the new database, new patterns will emerge to help characterize the “syndrome” of spinal cord injury. The power of combining sophisticated computer and statistical methods to sort through and organize vast quantities of information will allow scientists to build a larger picture of the epidemiology of spinal cord injury – not only a single result following an isolated insult, but a mosaic created from integrating the results of multiple functional and biological assays from many laboratories.

Ferguson was a postdoctoral researcher in the Beattie-Bresnahan laboratory at Ohio State University and moved with them to UCSF as an NIH fellow. He then obtained funding for his own laboratory through the NIH and other agencies and became an assistant professor of neurological surgery in 2010. Involved in both data science and wet lab science, Ferguson has since sponsored NIH and nonprofit fellowships for postdocs working in his laboratory and, together with his BASIC colleagues, is heavily invested in training the next generation

of neurotrauma researchers.

As with TBI, clinical trials for spinal cord injury have not produced new therapies for patients, but trials for spinal cord injury are made even more difficult due to the relative rarity of the condition. Michael Beattie and Director of Spinal Trauma, Sanjay Dhall, MD, are working to develop a California-wide network of leading hospitals and trauma centers for clinical and translational research related to spinal cord injuries. By developing joint infrastructure, the new network may be able to identify patients eligible for trial participation and route them to the appropriate treatment center. As with TRACK-TBI, the goal is to perform prospective data collection and create shared data repositories for neuroimaging, proteomic, and genetic biomarkers that may help inform prognosis and treatment. The big data analyses, led by Ferguson, could finally shed light on the poorly understood range of outcomes that can occur following contusions to the spinal cord.

In 2015, the Brain and Spinal Injury Center is home to nearly 50 multidisciplinary investigators working on the problem of translating research into meaningful differences for patients.

Vascular Neurosurgery

Faculty

Michael Lawton, MD
 Michael Huang, MD
 Arnau Benet, MD
 Jialing Liu, PhD
 S. Scott Panter, PhD

Recruited in 1997 to build the Department's Cerebrovascular Disease Program, Michael Lawton, MD became Berger's second faculty recruit – following famed pediatric neurosurgeon Warwick Peacock. Under the new chair's model of subspecialization, Lawton began to operate on every cerebrovascular case that came to the Neurological Surgery Department. This subspecialization paradigm immediately had a clear benefit: results in specific spheres continued to improve as individual surgeons took on more cases in their specialty.

During the 1990s, the Guglielmi Detachable Coil was introduced to treat aneurysms and created a shift away from more technically demanding microsurgical techniques towards endovascular coiling, which was primarily performed by interventional neuroradiologists. By the early 2000s, coiling was shown to be effective and safe in clinical trials and few neurosurgery programs were specializing in microsurgical clipping. It was during this time that Lawton not only continued to offer microsurgery, but also

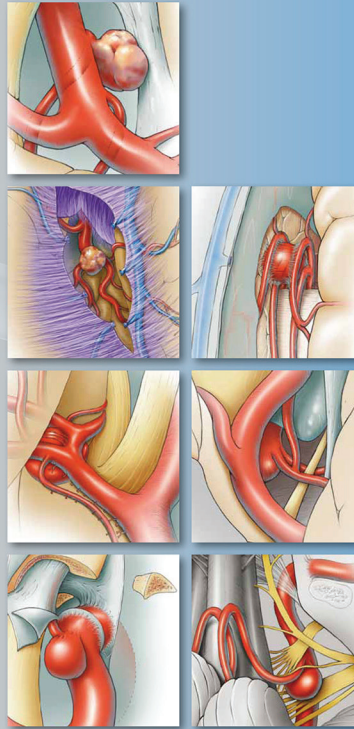
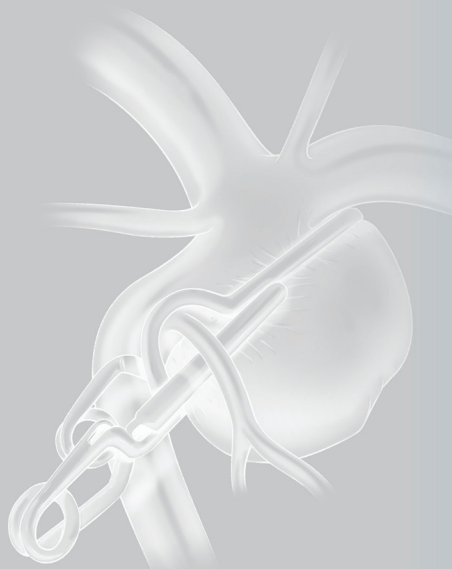
went about dramatically refining it. While coiling can be effective and safe, the response is not as durable. Successful clipping will restore proper blood flow through the artery and permanently repair the aneurysm. Predicting which aneurysms would be the best candidates for microsurgical clipping became a major focus of Lawton's clinical research.

For many years, treatment for aneurysms and arteriovenous malformations (AVMs) had been one-size fits all approach. Over his career, Lawton has defined the spectrum of these pathologies, publishing hundreds of scientific articles on clinical outcomes prediction based on various aneurysm and AVM subtypes and other patient-specific factors. His experience with nearly 3000 aneurysms and over 500 AVMs was eventually consolidated into two exhaustive, award-winning textbooks. *Seven Aneurysms: Tenets and Techniques for Clipping* and *Seven AVMs: Tenets and Techniques for Resection* have quickly become definitive guides to surgical techniques for these diseases. They each contain hundreds of original illustrations by medical illustrator Kenneth Xavier Probst, and systematically break down steps for treatment, serving as an invaluable resource for neurosurgeons looking to gain a higher level of expertise. *Seven Aneurysms: Tenets and Techniques for Clipping* was a finalist for

Seven Aneurysms

Tenets and Techniques for Clipping

Michael T. Lawton



 Thieme

Seven Aneurysms:
Tenets and
Techniques for
Clipping *written*
by Michael Lawton,
MD and published
by Thieme Medical
Publishers

the 2012 Ben Franklin Award in Professional/Technical Writing, and Kenneth Xavier Probst received an Award of Merit from the Association of Medical Illustrators for his illustrations.

Lawton also completed an endovascular fellowship at UCSF in 2011 to hone the coiling technique in order to be able offer patients the full spectrum of care. The same year, Michael

Huang, MD joined the Department after completing a fellowship in skull base and cerebrovascular surgery at the University of South Florida. Huang is primarily based at the Brain and Spinal Injury Center at San Francisco General Hospital operating on a wide range of hemorrhagic lesions and brain injuries. Today sixty to seventy percent of vascular cases referred to UCSF

Chief of Vascular Neurosurgery Michael Lawton, MD leads a group of volunteer neurosurgeons and healthcare providers to provide pro bono surgeries and train local neurosurgeons in the Philippines through the program Mission: BRAIN



Neurovascular Research

Stroke

are done within the Department of Neurological Surgery.

In 2011, together with former resident Alfredo Quinones-Hinjosa (currently the director of the Brain Tumor Center at Johns Hopkins), Lawton began annual trips to Guadalejara, Mexico to provide pro bono surgeries and free training to Mexican neurosurgeons. In 2014, that mission was expanded to the Philippines, where Lawton performed surgeries for six patients with cerebrovascular disorders, including those with aneurysms, arteriovenous malformations, and dural fistulas.

While Philip Weinstein's clinical practice was dedicated to spine surgery after the departure of Charles Wilson, he was focused on stroke in the laboratory. He was funded by the NIH to develop diagnostic techniques, such as MRI and other interventions, that could save tissue. Wanting to develop better techniques to improve outcomes, he conducted studies on how to protect the brain from blockage of an artery that would cause death and paralysis. In this area he was mentored by clinical faculty member Norman Chater, and was involved in developing an arterial bypass method in which an extra- to intra-cranial bypass would negate the impact of an arterial blockage. In 1983,

Chater published his outcomes for over 400 patients undergoing the microvascular extracranial-intracranial bypass for stroke.

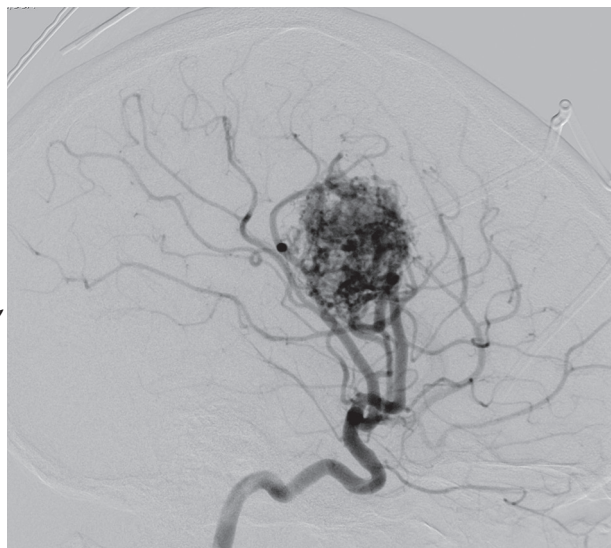
After receiving her PhD from Boston University in 1992, Jialing Liu took a position as a postdoctoral fellow in the Department of Neurology at UCSF. She eventually crossed over to the Department of Neurological Surgery in 1999 as an assistant researcher and began collaborating and publishing with Weinstein. Liu arose to the position of Associate Professor in 2005 and is currently the principal investigator of a lab funded by major grants from the NIH, the Department of Defense, and the Department of Veterans Affairs. In 2009, Liu received a VA Research Career Scientist Award. Her lab is located at the San Francisco Veterans Affairs Medical Center (SfVAMC) and focuses on determining the mechanisms mediating functional recovery and endogenous neural-stem-cell plasticity following cerebral ischemia and traumatic brain injury.

Also based at the SfVAMC, Scott Panter, PhD studies the role of iron, heme, or hemoglobin in central nervous system injury, using experimental systems including biochemistry, cell culture, and in vivo models to study this process of tissue damage. In 1993, he showed in mixed cultures of neurons and astrocytes that

hemoglobin causes neuronal injury, which was subsequently confirmed in the clinical trials of a hemoglobin-based blood substitute. He has developed models of subarachnoid and intracerebral hemorrhage, showing that hemoglobin causes significant infarcts and induces heat shock proteins. His laboratory also began developing new rodent models of focal and global ischemia and traumatic brain injury. These models were used to test intranasal delivery of chelators, such as deferoxamine, which was shown to reduce injury following stroke.

Center for Cerebrovascular Research

In 2000, William Young, MD was recruited from Columbia University to become a faculty member in UCSF's Department of Anesthesiology and Perioperative Care with a joint appointment in the Department of Neurological Surgery. That year, he established



Using the Lawton-Young grading scale, this ruptured left frontal arteriovenous malformation was defined as supplemented Spetzler-Martin grade 4: S2V0E1/A1B0C0

Arnau Benet, MD, works with resident Seunggu Han, MD at a surgical skull base anatomy course



the Center for Cerebrovascular Research (CCR), which brought together vascular specialists in a variety of disciplines to study genetics, epidemiology, and clinical course of these diseases, as well as develop computational models of cerebral circulation.

The new CCR quickly became successful at competing for national research grants, including several R01 awards and a Program Project Grant from the NIH. Lawton and Young collaborated on several investigations, including work looking at the basis of blood vessel malformations. In 2010, they published the Lawton-Young grading scale for AVMs to supplement the traditional Spetzler-Martin scale and better predict which lesions were amenable to surgery. It has since been validated in a multicenter study.

Young served as director of the CCR until his death in 2012, and together with Hua

Su, MD, developed the first animal model of brain AVM that recapitulated key features of the human disease. He also served as program director for the Brain Vascular Malformation Consortium, supported by the NIH Rare Diseases Network. The program examined several brain disorders linked to abnormal brain angiogenesis and associated with hemorrhagic stroke. After Young passed away, UCSF remained the coordinating center for the consortium, with Lawton at the helm. Lawton successfully competed for renewal of the \$6.5 million NIH grant in 2014, funding the consortium for an additional 5 years. Clinical and genetic information from patients at 10 primary sites is entered into a database that can be studied by researchers across institutions. By examining a large longitudinal cohort of patients with these rare diseases, Lawton and his colleagues hope to gather new

information to improve care for patients and develop consensus on optimal management.

Cerebrovascular and Skull Base Lab

In 2012, Arnau Benet, MD joined the Department of Neurological Surgery as director and principal investigator of the new Skull Base and Cerebrovascular Laboratory. Benet is an expert in 3D surgical anatomy and performed a fellowship at UPMC in minimally invasive skull base surgery in 2009, where he became particularly interested in pushing the boundaries of minimally invasive techniques in areas of the brain with very complex anatomy. Using cutting-edge technology, he has designed surgical simulation methods to accurately recreate operative scenarios in the laboratory, enabling him to compare approaches and design novel surgical trajectories. He has also designed a method for surgical simulation of challenging brain aneurysm surgery that includes 3D modeling and printing of aneurysm replicas from patients. His clinical research includes surgical outcomes and efficiency in neurosurgery and otolaryngology.

The Skull Base and Cerebrovascular Laboratory was a natural extension of the work Lawton began—striving to combine dexterity, experience, and technical expertise to provide the best outcomes to patients. In the new lab, residents and visiting scholars can improve their technique in a safe environment that accurately recapitulates

what they would encounter in an operating room. UCSF is now internationally recognized for its leadership in cerebrovascular surgery and each year ~ 30 physicians from all over the world come to observe techniques and procedures in both the operating room and the Cerebrovascular and Skull Base Anatomy Lab.

Epilepsy

Faculty

Edward Chang, MD

Scott Baraban, PhD

After an internship in general surgery and residency training in neurological surgery at UCSF, Nicholas Barbaro, MD joined the faculty of the UCSF Department of Neurological Surgery in 1985. He had specific interests in the treatment of disorders that are manageable by stereotactic and functional neurosurgical techniques, including epilepsy, chronic intractable pain syndromes, and movement disorders. Barbaro rose to Professor and Vice Chair in the department and became internationally recognized for his expertise in epilepsy. Surgeries for epilepsy included focal brain resections and disconnection operations, as well as implantation of vagus nerve stimulators.

During Barbaro's time as Chief of Epilepsy Surgery, UCSF established one of the first multidisciplinary care centers in Northern California for epilepsy

Nicholas Barbaro, MD served as Principal Investigator of the first multicenter, prospective trial of Gamma Knife radiosurgery for epilepsy



patients that combined the expertise of neurologists, neurosurgeons, neuropsychologists, and neuroradiologists. Clinical research included a trial of progesterone therapy for women with medically refractory epilepsy; a trial of deep brain stimulation to treat epilepsy; and neuroimaging studies using 7T MRI scanners and functional brain mapping techniques. The UCSF Epilepsy Center also served as the coordinating center for the Epilepsy Phenome/Genome Project sponsored by the NIH. Led by Daniel Lowenstein, MD in the Department of Neurology, the study collected detailed phenotypic and genomic information from patients with various types of epilepsy to identify

multigenic determinants of the underlying epilepsy syndrome.

In 2000, Barbaro became principal investigator of the first multicenter study in the U.S. to examine radiosurgery for medial temporal lobe epilepsy. Based at UCSF and funded by the NIH and the Elekta Corporation, the study was conducted at five centers and randomized patients into one of two radiosurgery dosage groups. Results of the trial were published in 2009 in *Annals of Neurology* and showed that radiosurgery for unilateral temporal lobe epilepsy resulted in seizure remission rates comparable to those reported previously for open surgery (temporal lobectomy was the standard of care). This paved the way for a larger clinical trial at 18 sites comparing radiosurgery to open surgery for epilepsy (ROSE). The ROSE trial has now finished accruing patients and long-term follow-up of these patients is currently underway.

In 2011, Barbaro left UCSF to become chair of neurosurgery at Indiana University and his practice was taken over by Edward Chang, MD. While a resident in the Department of Neurological Surgery at UCSF, Chang developed a special interest in surgical therapies for intractable epilepsy, advanced brain mapping methods, and the cortical mechanisms of language function. Under Barbaro and Chang, UCSF became a national leader in developing safer and more effective surgeries for epilepsy. Over 50 papers have

been published in the last ten years that review surgical outcomes and provide quantitative descriptions for how to improve patient selection and efficacy of treatment. This work has covered pathologies such as malformations of cortical development; temporal lobe epilepsy; and tumors and vascular lesions that cause seizures.

In 2012, Chang was the senior author of a landmark study revealing that epilepsy surgery is significantly underutilized in the United States. Tracking trends in epilepsy treatment in the United States over 20 years, the study showed that surgical cases had not increased despite clear evidence from randomized controlled trials demonstrating the effectiveness of surgery. While not all patients are surgical candidates, the study confirmed that there is a large, underserved population

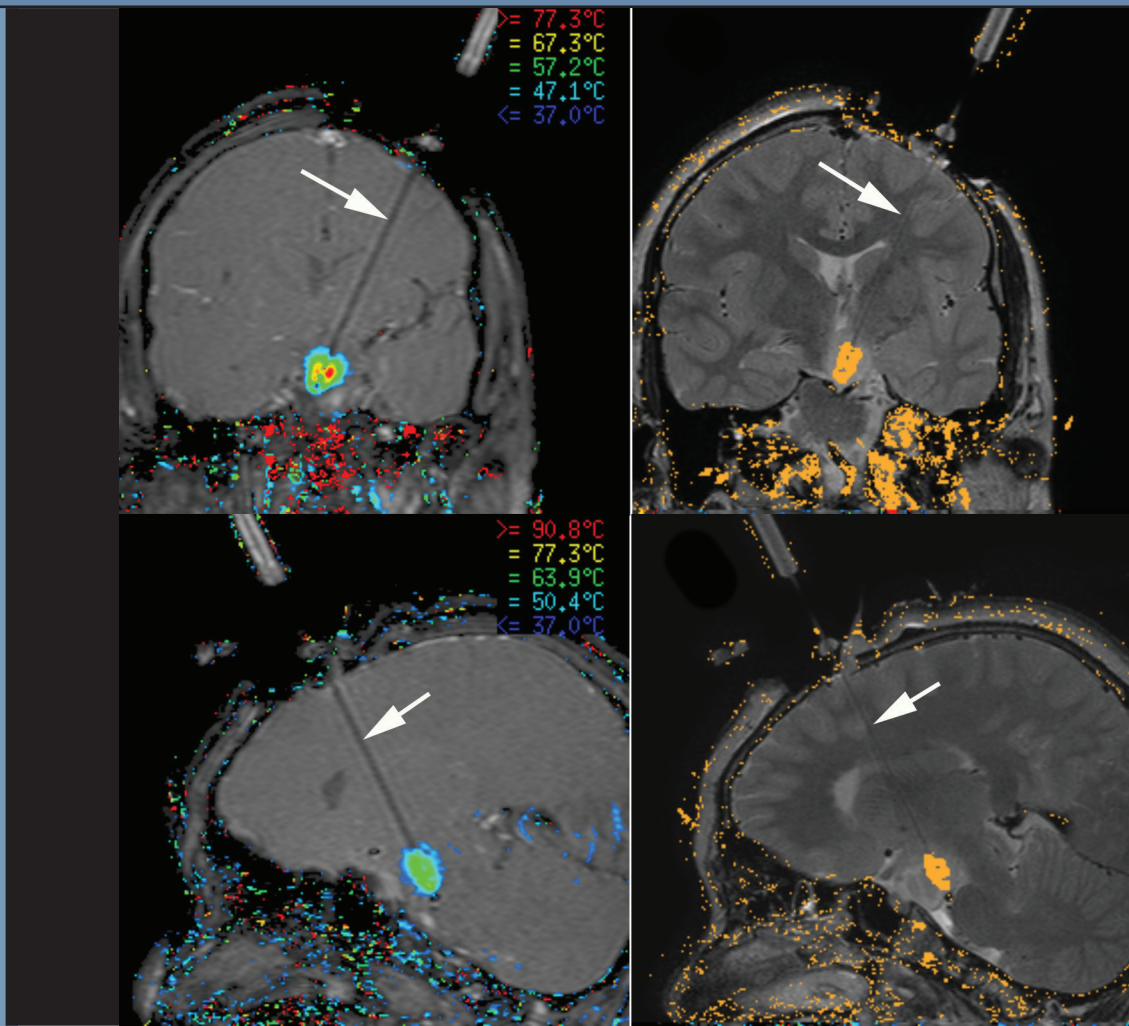
that suffers unnecessarily from impairing seizures. The report was coauthored by Dario Englot, David Ouyang, Nicholas Barbaro, and Paul Garcia, and earned Chang the prestigious Young Investigator Award from the American Epilepsy Society. Chang has also been the recipient of the NIH Director's New Innovator Award, Klingenstein Fellowship, Grass Foundation Young Investigator Award from the American Epilepsy Society, and, most recently, was named a Blavatnik National Laureate.

While surgical resection is still the best option for seizure control in many patients, new minimally invasive options have begun to emerge in recent years as alternatives to open surgery. In 2012, UCSF became the first hospital in the Bay Area to adopt the Visualase Thermal Ablation



Edward Chang, MD, Chief of Epilepsy Surgery, has been responsible for bringing new technologies to UCSF and leading several large outcome studies that demonstrate the safety and efficacy of surgery for many types of epilepsy

During laser surgery for epilepsy, thermal maps allow surgeons to monitor the temperature at the target and surrounding tissue, while tissue ablation maps show the extent of abnormal tissue being destroyed



System. This minimally invasive treatment involves guiding an MR-compatible laser applicator into the brain toward the target lesion that is the source of a patient’s seizures. The technique heats and destroys the small, well-defined area of abnormal brain tissue and leaves the surrounding tissue unharmed. The entire procedure is viewed in real time on MR images that show thermal maps displaying the distribution of heat to ensure safety and successful target treatment. UCSF currently has the largest experience with laser ablation for epilepsy in the Bay Area.

The UCSF Epilepsy Center is also one of few centers in the

nation to offer responsive neurostimulation (RNS) for treating adults with medication-resistant epilepsy—especially for those with seizures arising from more than one brain region or from brain regions that cannot be removed surgically. There is evidence that for some patients, using an implanted neurostimulator to treat seizures can be more effective than medications, and, because no brain tissue is removed, can involve less risk than other surgical options.

The underuse of epilepsy surgery for patients who may be good candidates can be partially attributed to ingrained patterns of care among primary care doctors, neurologists, and neurosurgeons that

do not always take into account the best available evidence. But another barrier is that identifying seizure foci is not always a straightforward task. Thirty percent of patients with epilepsy are diagnostically negative and 20% of MRI results that are positive for epilepsy are misleading.

If the source of the seizures is not a clearly focal lesion or if it is located in eloquent cortex, patients may be told that they are not surgical candidates.

In 2013, neurologist Robert Knowlton, MD joined the UCSF Epilepsy Center specializing in diagnosing complex cases of epilepsy, such as those that have no clear origin, and in identifying patients who could be successfully treated with surgery. Diagnoses are made based on the combined results of a variety of advanced diagnostic tests, including: high-density and video EEG, MEG, ictal SPECT, functional MRI, diffusion tensor imaging, PET, and MRI. The partnership of Knowlton and Chang has helped to identify and surgically treat many patients who may otherwise have continued to have seizures or take medications.

In 2014, the team further added to the cutting-edge diagnostic tools it uses with the addition of stereo-electroencephalography (SEEG) for select patients. This technology involves implanting depth electrodes through small openings in the skull that can precisely characterize the electrical activity of deep structures in the brain, detecting patterns of electrical abnormality that may not be found with a standard subdural grid.

Epilepsy & Speech Research

To provide the safest surgeries for patients with epilepsy, UCSF neurosurgeons implemented routine use of brain recordings to map functional cortex during resection of epileptic foci. During standard surgery for epilepsy, subdural grids are placed on the surface of a patient's brain to record patterns of electrical activity and avoid harm to areas of speech and language. As a result of these safety practices aimed at protecting a patient's ability to speak, Chang conducted research into speech mapping that began to shed light on the more basic question of how the brain organizes speech.

In volunteer patients already set to undergo epilepsy surgery, Chang recorded the electrical activity of their brains while they listened to recordings of English phrases and mapped when and where neurons were firing. The results showed that the brain organizes sounds based on how they are formed in the mouth (known to linguists as fricatives and plosives), which was previously unknown. The Chang lab now has the most detailed map of how speech sounds are produced in the human brain and how the brain identifies every speech sound in the English language.

This work—published in publications ranging from *Science* to the *New York Times*—has greatly expanded what we know about how the brain processes language. In a 2014 interview with the *San Francisco Chronicle*, Chang said “Our hope is that with

*Scott Baraban,
PhD, Principal
Investigator
at the UCSF
Epilepsy Center*



this more complete knowledge of the building blocks and fundamental aspects of language, we can meaningfully think about how learning occurs.”

Research into the Neurobiology of Seizures

There has also been a concerted effort in the department looking at the neural basis of epilepsy and how disrupted neural circuitry causes seizures. Scott Baraban joined the faculty in 1999, having received a PhD in pharmacology from the University of Virginia and postdoctoral training in the laboratory of Phil Schwarzkroin at the University of Washington—then one of the preeminent epilepsy research labs in the world. Baraban then went to Case Western Reserve University as an assistant professor of pediatrics and neuroscience before being recruited to UCSF to develop the epilepsy research program in neurosurgery. His early research in the department

centered on developing animal models for specific childhood seizure disorders and his laboratory focused on the hippocampus as a key structure in epileptogenesis. He and his colleagues soon discovered that clusters of displaced hippocampal neurons acted as a site of seizure initiation in vitro.

As with the other specialties under Mitchel Berger’s vision of basic science–clinician collaboration, Baraban also collaborated with Nicholas Barbaro and other clinicians specializing in epilepsy to study the epileptogenic properties of brain tissue obtained from patients undergoing epilepsy surgery, as well as research in rodent models of tuberous sclerosis. Over time his lab became especially known for its work in zebrafish models of epilepsy, and in 2012 Baraban was awarded a prestigious EUREKA grant from the NIH to study zebrafish mutants displaying a phenotype similar to monogenic epilepsy disorders primarily seen in children. The lab continues to use this model

to identify molecular targets for therapeutic treatment and screen drug candidates. In 2013 they discovered that the FDA-approved compound clemizole was able to prevent seizures in a zebrafish model of Dravet syndrome.

Baraban has also had a fruitful collaboration with famed stem cell scientist Arturo Alvarez-Buylla, PhD. Their laboratories initiated an exciting program aimed at generating interneurons from progenitor cells, which can then be transplanted into the brain to cure epilepsy. With funding from the NIH and the California Institute for Regenerative Medicine, the Alvarez-Buylla and Baraban laboratories have shown that progenitors derived from the medial ganglionic eminence region of adult mouse brains can be transformed into interneurons, produce the neurotransmitter GABA, and integrate into the neocortex to block spontaneous seizures. In a paper published in *Nature* in 2012, the UCSF

investigators demonstrated that there is a threshold for the number of interneurons that can survive and inhibit synaptic events after being transplanted. This implies that interneuron cell fate is intrinsically determined, independent of signaling from neurotrophic factors in the local environment. This finding challenged the long-held theory that interneurons are overproduced in the embryonic ventral forebrain and then migrate to the cortex where the excess cells are eliminated through competition for neurotrophic factors.

Baraban has been the recipient of many distinguished awards throughout his career and was most recently selected for the 2015 Javits Neuroscience Investigator Award by NINDS. This award is based on a Congressional mandate to support neuroscience research and acknowledges Baraban's long standing in the field as a distinguished scientist with a record of substantial contributions to the field of neuroscience.



The laboratory of Scott Baraban, PhD uses zebrafish to model rare types of pediatric epilepsy

Movement Disorders

Faculty

Philip Starr, MD, PhD

Paul Larson, MD

Edward Chang, MD

Daniel Lim, MD, PhD

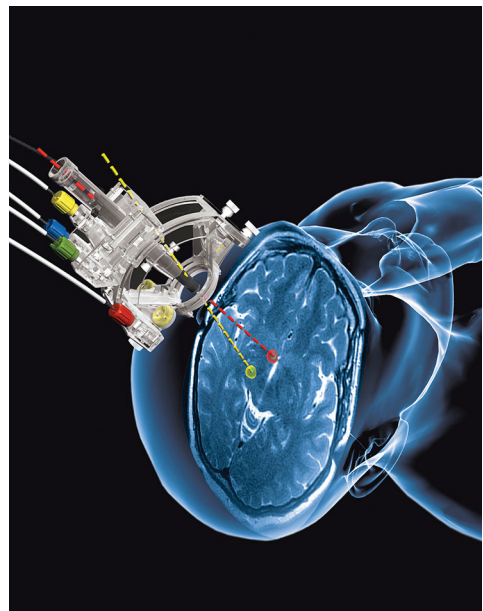
Phiroz Tarapore, MD

Krystof Bankiewicz, MD, PhD

In 1999 Philip Starr, MD, PhD joined the faculty at UCSF with a National Program Initiative Award to develop a center of excellence in the surgical treatment of movement disorders. Starr received his MD from Harvard Medical School with a concurrent PhD in neurobiology, and received fellowship training in microelectrode-guided surgery of movement disorders at Emory University when the technology was just beginning to become more widespread. Prior to 1997, movement disorders were primarily treated with medication and surgical treatment was an ablative procedure that destroyed normal brain tissue and could produce significant side effects. After FDA approval of the first deep brain stimulation (DBS) device in 1997, the surgical movement disorders program, based at the SFVAMC, rapidly became a leading center in the use and development of this new therapy. By 1999, it became the busiest program in the United States for the implantation of deep brain stimulators and was jointly led by Starr and neurologist William Marks Jr., MD.

In 2001, Paul Larson, MD joined the department following neurosurgical residency at the University of Louisville. During his residency Larson was extensively involved in the development of the Norton Hospital intraoperative MRI program, and spent a year in the Speed School of Engineering's Computer Vision and Image Processing Lab studying the basic science of CT and MR image analysis and 3D modeling. Shortly after arriving at UCSF, Larson began collaborating with Starr to develop real-time interventional MRI (iMRI) for the placement of deep brain stimulators.

In conjunction with Alastair Martin, PhD in the Department of Radiology, Jill Ostrem, MD in the Department of Neurology, and others, Starr and Larson developed a technique of implantation using a modified but commercially



ClearPoint, developed at UCSF, uses an MR-compatible frame for precise stereotactic neurosurgical procedures



*Philip Starr, MD, PhD
uses the ClearPoint
system to perform
deep brain stimulation
surgery inside an
MR scanner*

available skull-mounted aiming device and custom-made, MR-compatible surgical instruments. The procedure was done inside the MR scanner, allowing the surgeons to guide electrodes under direct visualization without the need for microelectrode recording or a stereotactic frame. Previously patients would need to be awake to confirm correct placement of the electrodes, but iMRI placement allowed them to be under general anesthesia.

In 2008, the Surgical Movement Disorders team partnered with the medical device company SurgiVision to develop new technologies for the iMRI DBS technique. This included an MRI-compatible, skull-mounted aiming device and MR coils specifically designed to provide optimal imaging during surgery. They also developed a software environment that standardizes

the implantation procedure on different MRI platforms. The system was named ClearPoint and was approved by the FDA in 2010. The new technology obviated the need for a stereotactic frame, reduced the number of brain penetrations to one, and shortened operating times. Today it is used in many other neurosurgical centers across the country. The system also has applications for delivering therapeutic drugs to precise structures of the brain and monitoring their distribution.

After the introduction of DBS for surgical treatment of movement disorders, it quickly became the gold standard. However, there had been continued debate over which area of the brain was best to stimulate: the globus pallidus interna (GPi) or the subthalamic nucleus. Marks, Ostrem, and Starr became investigators of a six-center study—and the largest

Directors of the Surgical Movement Disorders Center Jill Ostrem, MD and Philip Starr, MD, PhD (left) with Bachmann-Strauss Foundation president Bonnie Strauss and Chair of Neurological Surgery Mitchel Berger, MD. In 2013, the Surgical Movement Disorders Center at UCSF became the fourth Bachmann-Strauss Center of Excellence in the nation



study of DBS for Parkinson's disease every performed—to answer this question. Published in the *New England Journal of Medicine* in 2010, the results showed that the globus pallidus interna (GPi) and the subthalamic nucleus were equal in motor benefit, but the GPi was slightly safer for patients with impaired cognitive function or depression. The findings led to changes in the way DBS surgery is performed for patients with those symptoms.

DBS has also been used to treat other neurological and neuropsychiatric conditions, and neurosurgeons at UCSF have been at the forefront of off-label studies for these conditions. Patients with severe depression, obsessive-compulsive disorder, Tourette's syndrome, and cluster headache have all been treated with DBS at UCSF.

Today, the Surgical Movement Disorders Center is home to 27 members and is the largest

program of its kind in Northern California. Over 1500 DBS systems have been implanted since 1998. The affiliated program at the SFVAMC is one of only six Parkinson's Disease Research, Education, and Clinical Centers established by the U.S. Department of Veterans' Affairs.

There are currently six functional neurosurgeons in the Department: Philip Starr, Paul Larson, Daniel A. Lim MD, PhD; Edward Chang; and Phiroz Tarapore MD. They frequently collaborate with members of the Department of Neurology and with neuropsychologist Caroline Belkoura, PhD, who provides baseline neuropsychological assessments for patients prior to surgery, as well as ongoing monitoring of cognitive function over time. The results of these evaluations are used to assist with treatment planning and return-to-work strategies.



The Bankiewicz Lab in 2015. From left to right: Lluis Samaranch, John Bringas, Waldy San Sebastian, John Forsayeth, Krystof Bankiewicz, Phil Pivrotto, Piotr Hadaczek, Michael Macayan. Not pictured: Agnieszka Ciesielska, Janine Beyer, and Marin Thompson

Movement Disorders Research

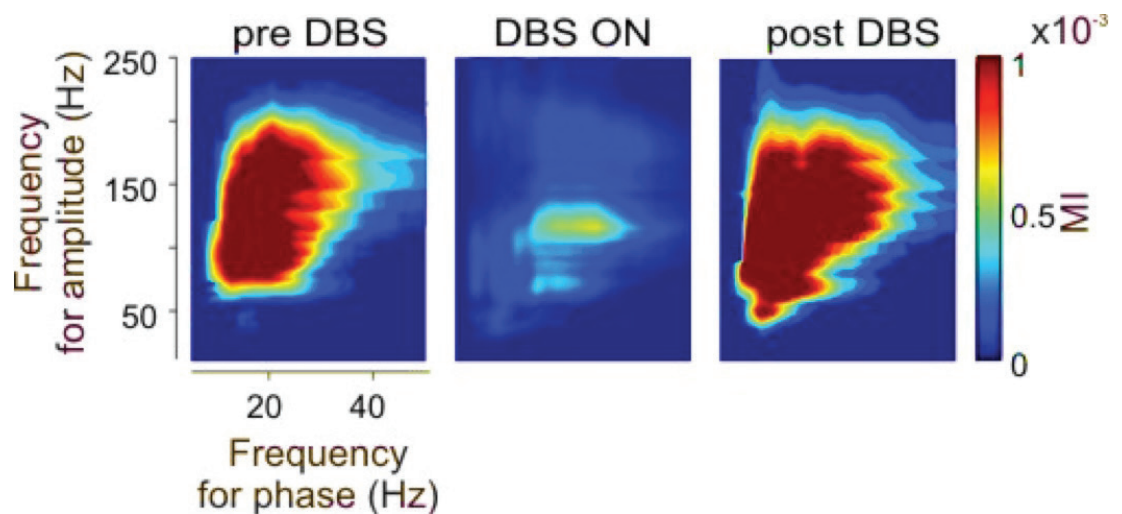
The Surgical Movement Disorders Center currently has 23 ongoing research protocols, including several aimed at identifying genetic variance among patients with movement disorders to improve prognosis, predict response to treatment, and identify new therapeutic targets. The group of over 27 members is actively engaged in translational research that can be applied to clinical use.

But the modern movement disorders research program at UCSF began with Rob Turner, PhD and Krystof Bankiewicz, MD, PhD in the early 2000s. Turner, who was a faculty member from 2000 to 2006, focused on defining the role of frontal cortex and basal ganglia in motor control, quantitatively defining brain areas that produce optimal therapeutic effects in response

to stimulation for movement disorders, and evaluating pallidal surgery as therapy for dystonia.

Bankiewicz, who came to UCSF in 1998, had rich interests in drug delivery technology and the development of clinically relevant animal models for both brain tumors and movement disorders. Over the last 17 years, his laboratory has significantly advanced the technology of convection-enhanced delivery (CED), which is used to deliver therapies directly into the brain, circumventing the blood-brain barrier. CED uses a pressure gradient at the tip of the cannula to push interstitial fluid out of the way, enabling coverage of larger brain volumes than could be achieved by diffusion alone. The current research program of the Bankiewicz laboratory includes therapies

Analyzing electrocorticographic recordings of neuronal populations, investigators in the laboratory of Philip Starr, MD, PhD are finding distinctive patterns of brain synchronization in patients with movement disorders



for Parkinson's disease, brain cancer, Niemann-Pick disease, dyskinesias, and AADC deficiency.

Using a nonhuman primate model of Parkinson's disease, Bankiewicz and his colleagues have shown that the transfer of the gene that codes for amino acid decarboxylase (AADC) into the striatum restored the production of dopamine in the brain (by converting levodopa to dopamine). The primates exhibited strong expression of AADC activity eight years after infusion, and these results were published in 2010 together with Pitor Hadaczek, PhD, John Forsayeth, PhD, and others. Bankiewicz and his colleagues also pioneered technology to monitor delivery of agents into the brain of primates in real time using MRI, which was the basis of the work for ClearPoint. Bankiewicz's group has also studied gene transfer of a growth factor (GDNF) that has shown promise in restoring function in Parkinson's disease, and is currently evaluating

it in primate models.

In a striking example of the translational research done in the department, the studies of AAV2-AADC in primates have now been translated into the phase I gene therapy trial currently being performed for human patients with Parkinson's disease, led by Bankiewicz and Paul Larson. The trial combines convection-enhanced delivery of AAV2-AADC and ClearPoint to optimize distribution of the infusate and, if successful, the therapy will decrease patients' dependence on medication and improve symptoms.

The laboratory of Philip Starr uses electrocorticography, widely used in epilepsy, to study the underlying pathophysiology of movement disorders. In 2012, Starr and postdoctoral fellow Coralie deHemptinne, PhD showed that in Parkinson's disease, population spike activity in primary motor cortex is excessively coupled to the phase of low frequency rhythms,

and this pathological oscillatory synchronization is ameliorated by DBS. This important finding not only reveals fundamental mechanisms by which basal ganglia disease disrupts cortical function, but gives novel insight into mechanisms of deep brain stimulation. Starr and deHemptinne hypothesize that the electrical pulses from the DBS device may control movement disorder symptoms by decoupling population spiking and return neuronal firing to a more normal pattern.

In a pilot trial initiated in 2014, the Surgical Movement Disorders group began implanting the Activa PC+S pulse generator into patients. This new implanted pulse generator stores local field potentials to allow chronic brain recording with wireless, noninvasive data downloading. The UCSF group was the first to implant a chronic, multisite brain-recording device in a patient with Parkinson's disease. The ultimate goal of the trial is to refine the next generation of DBS devices so that they can incorporate the data stored in the implanted pulse generator and create a feedback-controlled system similar to today's pacemakers. Instead of sending out a constant electrical signal, the device would self-regulate and only put out an electrical pulse when it is needed and symptoms are present.

One of the most surprising developments to emerge from the surgical movement disorders program has been the application of DBS for tinnitus. In 2011, Paul Larson and otolaryngologist

Steven Cheung, MD demonstrated that stimulation in a newly discovered region of the caudate nucleus called area LC could modulate loudness of auditory phantoms or create phantoms where none had previously existed. Area LC was not previously thought to be involved in auditory perception, prompting a new model for how the brain perceives sound. Based on this work, Drs. Cheung and Larson launched the first clinical trial of DBS for patients with the most severe forms of tinnitus who have not been helped by other treatment modalities.

While functional neurosurgeon Phiroz Tarapore was a resident in the Department of Neurological Surgery, he developed a strong research interest in functional imaging and presurgical mapping with transcranial magnetic stimulation (TMS). In collaboration with Sri Nagarajan, Director of the Biomagnetic Imaging Laboratory, he worked to develop and validate techniques for mapping cortical regions associated with motor and speech pathways using magnetoencephalography, and established the first protocols for using navigated TMS for presurgical speech and motor mapping at UCSF. Upon graduating from residency in 2013, Tarapore joined the faculty, and he continues to pursue his research as the head of the new Core Facility for Navigated TMS. This exciting new project makes TMS-based mapping available to the UCSF community, both inside and outside the Department of Neurological Surgery.

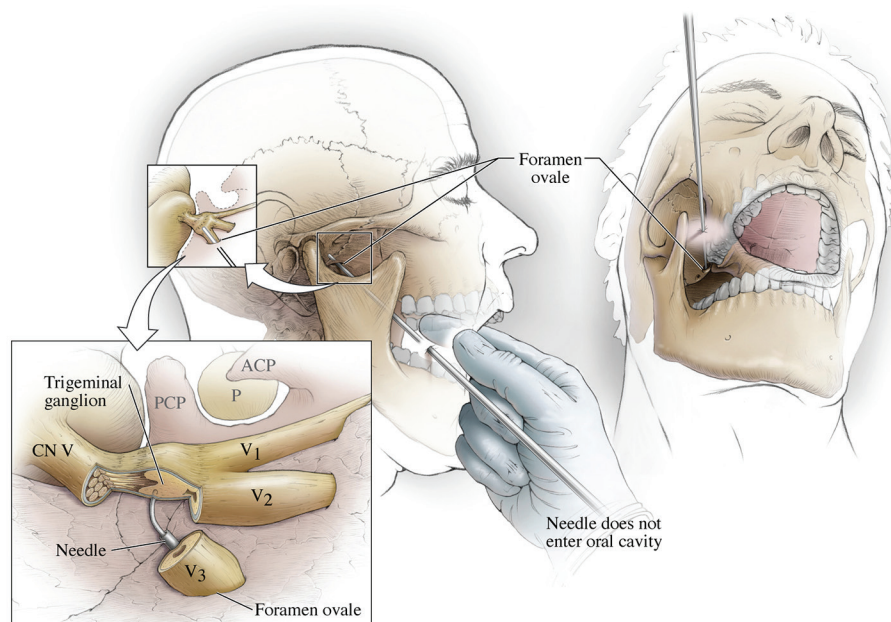
Pain and Peripheral Nerve Surgery

Faculty
Line Jacques, MD

The relevance of neurological surgery in pain management is inherent in the way transmission of pain signals occur through the peripheral nervous system. Through the development of specialized surgical procedures, from intrathecal opiate pumps to spinal cord stimulators, neurosurgeons have long played a major role in delivering pain control. In the early 2000s, peripheral nerve disorders and pain syndromes were treated by specialists Nicholas Barbaro, MD and Luc Jasmin, MD, PhD. Jasmin was focused primarily on treating patients with chronic neuropathic pain syndromes

using electrical stimulation of the spinal cord, motor cortex stimulation, and intrathecal delivery systems to treat cancer pain. He was also the principal investigator of a laboratory that used animal models to investigate the neuroanatomy and neuropharmacology of pain and inflammation.

Barbaro became an expert in the difficult diagnosis of various facial pain disorders, many of which are still poorly understood today. Treatment for trigeminal neuralgia could still be achieved with microvascular decompression or radiofrequency lesioning, as it had been under John Adams, but Gamma Knife radiosurgery also became a popular, less invasive option. Patients began traveling from other areas of the country to be evaluated at UCSF for severe facial pain and for the full spectrum of surgical and nonsurgical options offered through the multidisciplinary



Radiofrequency thermocoagulation for trigeminal neuralgia (image by Kenneth Xavier Probst)

UCSF Pain Center.

When Barbaro left UCSF in 2011 to become chair of neurosurgery at Indiana University, the trigeminal neuralgia practice was led by Edward Chang, MD. In 2014, Line Jacques, MD was recruited from McGill University—Montreal Neurological Hospital to rebuild the peripheral nerve program and pain program. While the facial pain clinic had been successfully absorbed by Chang, the department needed growth in the area of complex regional pain syndromes, which had been handled by a variety of specialists at the UCSF Pain Center.

Jacques received fellowship training in peripheral nerve surgery from Louisiana State University under David Kline, MD and amassed 17 years of experience in pain and peripheral nerve surgery at McGill University. Her clinical specialty interests are in the treatment of entrapment syndromes, peripheral nerve tumors, and reconstructive procedures of the peripheral nerves and brachial/lumbosacral plexus.

Neuroimaging and nerve conduit studies have been the biggest technological developments in treating nerve injuries over the last decade. Imaging of the nerves has also become an important part of planning surgery and predicting recovery from injury. The advanced neuroimaging group at UCSF is key to helping surgeons tackle these problems. Techniques such as diffusion tensor imaging and MR neurography allow visualization of the nerve fibers and can reveal



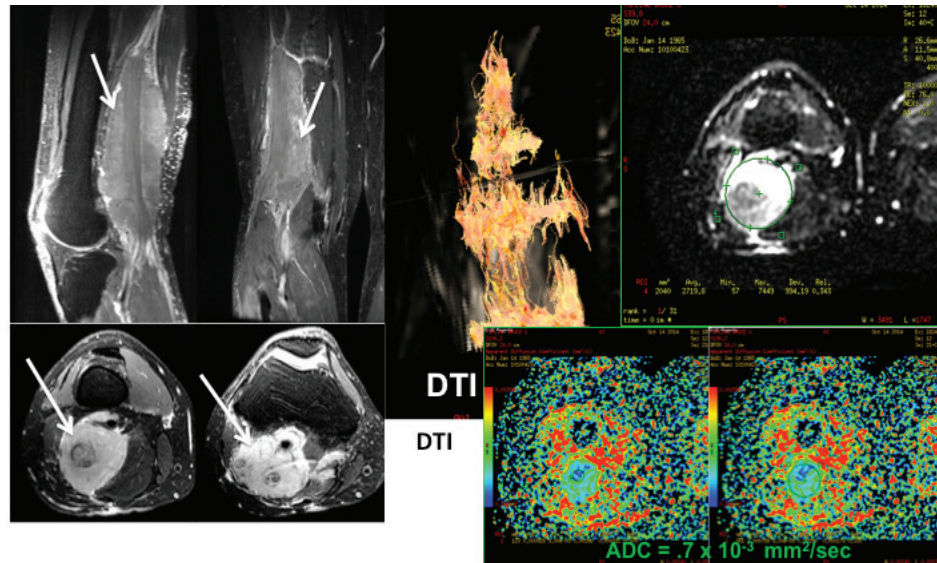
*Line Jacques, MD
became Chief of
Peripheral Nerve
and Pain Disorders
Surgery in 2014*

evidence of axonal regeneration.

Jacques also has extensive expertise in the treatment of chronic, refractory, peripheral neuropathic pain, including the use of spinal cord stimulation in patients with failed back surgery syndrome, complex regional pain syndrome, and peripheral vascular disease; occipital nerve stimulation for the treatment of migraines; and implantable drug delivery systems for the treatment of nociceptive pain and movement disorders.

Jacques has a strong interest in functional outcomes research, which she has brought to UCSF. In a 2014 interview, she said, “Validated tools like questionnaires can often help us determine whether the patient can be managed with nonsurgical therapies, or if neuromodulation fits into their treatment. Most of these patients have been in chronic pain for a significant length of time before they navigate their way to our clinical program, which has a

UCSF neuroradiologists and neurosurgeons use diffusion tensor imaging to assess nerve damage caused by peripheral nerve sheath tumors and to plan more precise surgeries to remove the tumors and preserve function



significant impact on their quality of life. Being able to manage their pain and return their quality of life is very rewarding for our team.”

In a pilot trial, functional neurosurgeon Paul Larson has also performed several cases of deep brain stimulation for patients with medically refractory cluster headaches. When unresponsive to medication, cluster headache may cause enormous suffering and disability. DBS of the hypothalamus, which is abnormal in patients with cluster headache, shows promise for treating this disorder.

Center for Neural Engineering and Prostheses

Faculty

Edward Chang, MD
Jose Carmena, PhD
(UC Berkeley)

In 2010, the Center for Neural Engineering and Prostheses (CNEP) was born from a new partnership between UCSF and UC Berkeley. Co-directed by UCSF neurosurgeon Edward Chang and UC Berkeley engineer Jose Carmena, the center integrated cutting-edge electrical and neural engineering with world-class basic and clinical neurosciences to develop technology to restore sensory, motor, and cognitive function in patients suffering from disabling neurological conditions. Specifically, researchers at CNEP became focused on trying to understand neural networks

to develop brain-machine interfaces that can convert the thoughts of patients who are paralyzed into commands for a robotic limb or skeleton.

As the technology for recording electrical activity directly from the brain continues to improve, researchers at UCSF and elsewhere have been able to refine their understanding of how the brain is organized and processes the external environment. By creating a device that combines visual, tactile or auditory feedback, modulation of neural network activity may be achieved, allowing more refined control of the neuroprosthetic.

Recently, there also has been an interest in how this technology can be applied to neuropsychiatric disorders. Deep brain stimulation for depression and OCD has been used with some success, but remains a relatively crude tool for treating these complex disorders.

In 2014, the CNEP team was awarded a \$26 million grant to map the human brain circuits that go awry in neuropsychiatric disorders, such as depression, anxiety, and posttraumatic stress disorder, and develop a new generation of biomedical devices for treatment. The investigators, led at UCSF by Edward Chang and Philip Starr, are using multisite electrode recordings to create a high-resolution map of the human mesolimbic circuitry in both normal patients and those with neuropsychiatric disorders. Instead of focusing on specific neurotransmitters to target with drugs, the researchers seek to understand these disorders as disruptions of

a highly coordinated network.

As disrupted circuits specifically associated with neuropsychiatric disorders become defined, the research team will begin to develop a precise stimulation therapy that guides the brain to strengthen alternative circuits. By leveraging the brain's natural capacity for neural remodeling and learning, this approach will potentially allow the newly strengthened circuits to bypass the disease-associated signals and thereby eliminate symptoms. The new therapy would come in the form of an implanted device that could record spatiotemporal patterns of neural activity and modulate the brain when it detects a pattern of abnormality consistent with the patient's disorder.

The ambitious project is funded by the Defense Advanced Research Projects Agency, a major partner in support of President Obama's Brain Initiative, under the agency's recently launched SUBNETS (Systems-Based Neurotechnology for Emerging Therapies) program. The project also involves more than a dozen scientists, engineers and physicians at CNEP, Lawrence Livermore National Laboratory, Cornell University, and New York University, as well as industry partners.

Pediatric Neurological Surgery

Faculty

Pediatric Neurological Surgery

Nalin Gupta, MD, PhD

Kurtis Auguste, MD

Mitchel S. Berger, MD

Corey Raffel, MD, PhD

Ronald Shallat, MD

Peter Sun, MD

Pediatric Neuro-Oncology

Anuradha Banerjee, MD, MPH

Sabine Mueller, MD, PhD

Theodore Nicolaides, MD

Michael Prados, MD

Mitchel Berger's first faculty recruit in 1997 was renowned pediatric neurosurgeon Warwick Peacock, MD. A native of South Africa, Peacock's expertise was in the surgical treatment of intractable epilepsy and spasticity. During his career he had one of the largest series of operations for epileptic seizures in children of any surgeon in the world, having performed more than 80 hemispherectomies, as well as lobectomies and focal resections, and disconnective procedures including corpus callosal resection and multiple subpial transections to disrupt abnormal brain electrical activity.

The surgical treatment of epilepsy also made possible basic science research into the mechanisms of epileptogenesis. Peacock and his colleagues were one of the first groups to show data indicating the intrinsic

electrical properties of neocortical neurons from children vary according to cell morphology and change with increasing age.

Peacock is also internationally recognized for developing a safe and effective surgical procedure now used widely to treat spasticity in children who have cerebral palsy – selective posterior rhizotomy. He and his colleagues modified an earlier posterior rhizotomy procedure that had been used for nearly a century in order to better identify the sacral nerve roots when performing an L2 to S1 laminectomy, thereby preserving bowel and bladder function. In certain patients with cerebral palsy, selective dorsal rhizotomy can improve range of movement and function.

In the late 1990s he described standard methods for nerve rootlet testing and selection through electromyographic monitoring.

In addition to being Chief of Pediatric Neurosurgery at both UCSF and UCLA, Peacock held UCSF's Dennis Bruce Dettmer Professorship of Pediatric Neurosurgery. In 2001, he became Professor Emeritus, but retains an interest in teaching and research. He has been called a master educator by many of his colleagues and has embodied UCSF's triple mission in clinical excellence, research, and education.



*Chief of Pediatric
Neurological Surgery
Nalin Gupta, MD, PhD
with pediatric nurse
practitioner Caroline
Pearson, RN, PNP*

Pediatric Brain Tumor Program

In 2001, the Pediatric Neurological Surgery program was assembled with new faculty and a close association with other pediatric specialties. Directed by Nalin Gupta, MD, PhD, a former BTRC research fellow and graduate of UCSF's biophysics PhD program, the team included chairman Mitchel Berger and pediatric neurosurgeon Victor Perry, MD. Both Gupta and Berger completed pediatric neurosurgery fellowships at the Hospital for Sick Children in Toronto, Canada. Working with them to treat children with brain tumors were pediatric neuro-oncologists Anuradha Banerjee, MD, MPH, who also brought a special interest in palliative care, and Michael Prados, MD, director of neuro-oncology and PI for the Pediatric Brain Tumor Consortium, a national clinical

trials group. Prados has received world-wide recognition for his work with both adult and pediatric brain tumors and in 2014, his career was recognized with the Victor Levin Award in Neuro-Oncology Research from the Society for Neuro-Oncology.

The clinical trials program has been a particular strength of the pediatric neuro-oncology program. The Department participates in phase I and II trials of promising therapeutic drugs, new biological therapies, treatment delivery technologies, and radiation treatment strategies for all types of newly diagnosed and recurrent CNS tumors. Pediatric neurosurgeons and neuro-oncologists at UCSF have had a long history of conducting trials in coordination with the Pediatric Brain Tumor Consortium, the Children's Oncology Group, as well as with leading biotechnology companies. Many early trials for pediatric brain tumors focused

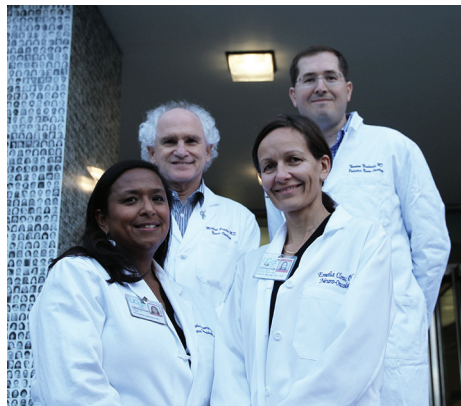
on optimizing radiation and chemotherapy regimens. However, as with other types of cancers, modern efforts to treat pediatric brain tumors are increasingly focused on targeted therapies and personalized medicine.

In 2010, board-certified pediatric neuro-oncologists Theodore Nicolaides, MD and Sabine Mueller, MD, PhD joined the pediatric brain tumor program. Nicolaides began collaborating with C. David James, PhD and Prados to study inhibitors of mutant BRAF, which is present in a large fraction of pediatric brain tumors. This work eventually became a project in UCSF's Brain Tumor SPORE portfolio in 2013 and was the first pediatric project of any Brain Tumor SPORE program in the nation. A clinical trial of the BRAF inhibitor vemurafenib is now underway in children with astrocytomas

Mueller's special interest in palliative care and late effects of therapy also led to the launch of studies into improving long-term cognitive and social functioning, as well as quality of life.

In 2012, Mueller and Prados spearheaded a new clinical trials group, the Pacific Pediatric Neuro-Oncology Consortium (PNOC), made up of 11 children's hospitals that focused on developing strategies based on the biology and genetics of a patient's individual tumor. As an example, PNOC is leading the first pilot study of individualized therapy for diffuse intrinsic pontine glioma; based on the molecular profile of the patient's tumor, a specialized tumor board recommends treatment after considering all FDA-approved drugs to target the specific abnormalities found in that tumor. PNOC investigators are also interested in moving the most promising laboratory findings from their respective institutions into phase I trials that can be performed across institutions, such as the BRAF inhibitor trial developed by Nicolaides. The work done at UCSF and PNOC (now comprising 15 sites) will provide evidence for whether individualized therapies improve survival odds beyond those achieved with generalized therapies.

Pediatric neuro-oncologists Anuradha Banerjee, MD, MPH, Sabine Mueller, MD, PhD, Michael Prados, MD, and Theodore Nicolaides, MD



Landmark Pediatric Neurosurgical Trials

UCSF has been involved with some of the greatest innovations in pediatric neurosurgery over the last decade. The birthplace of fetal surgery, UCSF participated in the first clinical trial of fetal surgery for myelomeningocele, which is a condition usually



*Nalin Gupta, MD, PhD,
performing surgery
for a pediatric brain
tumor causing epilepsy
in a young patient*

discovered during the second trimester. The Management of Myelomeningocele Study was a randomized surgical trial that determined in utero surgery resulted in fewer neurological complications than surgery after birth, as well as improvements in the infant's mental development and motor function. The results were published in the *New England Journal of Medicine* in 2010. UCSF is the only institution west of the Rockies to offer this type of surgery.

Gupta and Chief of Neonatology David Rowitch, MD, PhD also led one of the first neural stem cell transplantation trials ever conducted in the United States—a phase I trial for Pelizaeus-Merzbacher disease, which prevents the formation of myelin in children and leads to fatality. Although only a safety and preliminary efficacy study, the results, published in *Science* in

2012, showed that human neural stem cells (developed by Stem Cells, Inc.) can successfully engraft into the brains of patients and MR diffusion data suggested that the transplanted cells produce myelin in the white matter.

Pediatric Epilepsy Program

The special expertise in pediatric epilepsy established by Peacock continues at UCSF today. As with adult epilepsy, it is increasingly recognized that surgery may provide permanent freedom from seizures for many children.

Kurtis Auguste, MD graduated from the department's residency program in 2007. In 2008, he returned from a one-year fellowship in pediatric neurosurgery at the Hospital for Sick Children in Toronto, Canada to become the director

of the Pediatric Epilepsy Surgery Program at UCSF and Oakland Children's Hospital. Auguste closely collaborates with pediatric epileptologist Joseph Sullivan, MD in the Department of Neurology to identify patients who are surgical candidates. In addition to standard resection, some patients have the option of undergoing minimally invasive laser surgery. UCSF has done more laser ablation surgeries for pediatric epilepsy than any other center in California. More than 40 procedures for pediatric epilepsy are performed each year at UCSF, which is one of the highest volumes in the nation for this subspecialty.

In an ongoing effort to provide noninvasive alternatives to children undergoing brain surgery, Auguste has also led the adoption of transcranial magnetic stimulation (TMS) to map cortex. TMS is currently used as a preoperative adjunct to other well-established techniques, but UCSF is leading a comparison to validate the technique and determine whether it can replace other mapping techniques for select patients without sacrificing precision.

Collaborative Care

Other services that the pediatric neurosurgery program has particular strengths in include cerebrovascular surgery, craniofacial syndromes, complex spine disorders, and movement disorders. On the vascular

team, Michael Lawton provides expertise alongside two pediatric neurologists, Heather Fullerton, MD and Christine Fox, MD, who are among the few experts in the United States with specialized training in pediatric stroke and cerebrovascular disease. Patients with complex spine disorders may be seen by neurosurgeons and orthopaedic surgeons, as well as skilled inpatient rehabilitation specialists.

In *Journal of Neurosurgery: Pediatrics*, Philip Starr, co-director of UCSF's Surgical Movement Disorders Center, and his team have published one of the largest case series of deep brain stimulation for pediatric dystonia and movement disorders worldwide. Deep brain stimulation is used to treat both primary and secondary dystonia and rarer diseases like essential tremor and juvenile Parkinsonism. It can also be used to treat patients who are not helped by medications or who cannot tolerate the severe side effects of medications.

UCSF Children's Hospital Expansion to Oakland and Mission Bay

In 2014, the UCSF Benioff Children's Hospital and Children's Hospital & Research Center Oakland became united following a \$100 million donation by philanthropists Marc and Lynne Benioff. Now called the UCSF Benioff Children's Hospitals, these two leading children's



The new UCSF Benioff Children's Hospital opened its doors in 2015, providing a state-of-the-art facility to house all pediatric specialties at UCSF

hospitals are providing more coordinated, comprehensive care to children across the Bay Area. The pediatric neurosurgery program in Oakland is led by Peter Sun, MD, and has special expertise in hydrocephalus, spasticity, and craniofacial abnormalities. UCSF Benioff Children's Hospital Oakland is also home to state-of-the-art rehabilitation programs to provide full continuity of care for patients who have undergone neurosurgery.

In 2015, UCSF Benioff Children's Hospital San Francisco opened the doors of its new home at the UCSF Mission Bay campus. The state-of-the-art hospital features the most advanced treatment technologies and is the central location of the Pediatric Brain Center, which includes over 20 subspecialty clinics and centers dedicated to individual pediatric neurological

disorders, such as brain tumors, concussion, neurofibromatosis, brachial plexus and nerve injury, and epilepsy. Whenever possible, patients and their families meet with all the specialists they need to see on the same day.

The improvements in operating room technology that have been seen with adult specialties have also carried over to pediatric neurosurgery. The new hospital at Mission Bay is equipped with intraoperative MRI and the latest in neuronavigation, cranial nerve monitoring, and ultrasound. Functional imaging with fMRI, diffusion tensor imaging and MR spectroscopy are also routinely used to devise tailored treatment plans. *US News & World Report* has consistently named the Pediatric Neurosurgery Service at UCSF among the best in the nation.

Brain Tumor Center

Faculty

Brain Tumor Surgery
 Mitchel S. Berger, MD
 Manish Aghi MD, PhD
 Sandeep Kunwar, MD
 Michael McDermott, MD
 Philip Theodosopoulos, MD

Adult Clinical Neuro-Oncology

Susan Chang, MD
 Michael Prados, MD
 Nicholas Butowski, MD
 Jennifer Clarke, MPH, MD
 Jennie Taylor, MPH, MD

Pituitary Endocrinology

Lewis Blevins Jr., MD

Brain Tumor Research Center

Arturo Alvarez-Buylla, PhD
 Krystof Bankiewicz, MD, PhD
 Gabriele Bergers, PhD
 Joseph F. Costello, PhD
 Aaron Diaz, PhD
 John Forsayeth, PhD
 Jeanette Hyer, PhD
 Annette M. Molinaro, PhD
 Theodore Nicolaides, MD
 Hideho Okada, MD, PhD
 Arie Perry, MD
 Claudia Petritsch, PhD
 Joanna Phillips, MD, PhD
 Russell O. Pieper, PhD
 Kyle Walsh, PhD
 John Wiencke, PhD
 Margaret Wrench, PhD
 Shichun Zheng, MD

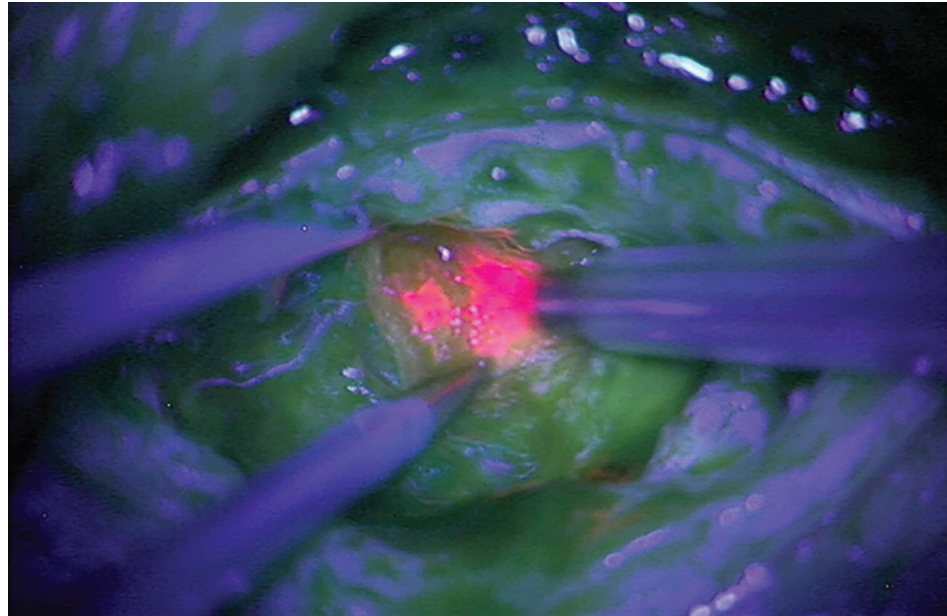
The largest group of clinicians and scientists in the Department of Neurological Surgery at UCSF is devoted to brain tumors. The Brain Tumor Center tightly integrates surgery, clinical oncology, and research and continues the tradition of translational research that it was developed on. This group also has close ties with faculty in the Departments of Radiation Oncology and Radiology, many of whom also have joint appointments in Neurological Surgery.

Surgery

Chair Mitchel Berger, MD is internationally recognized for pioneering techniques in the field of brain mapping. This subtle art uses electrical stimulation to identify functional areas of cortex, allowing surgeons to achieve a greater extent of resection in either cerebral hemisphere, and especially enhancing resection of surrounding nonfunctional tissue that may harbor residual tumor cells that could cause recurrence. Berger and his colleagues have unequivocally shown that a greater extent of resection can increase survival for patients with both low-grade and high-grade glioma, making precise brain mapping a critical component of surgery for these tumors.

In 2008, together with Nader Sanai, MD and Zaman Mirzadeh,

5-aminolevulinic acid guides surgeons to tumor cells that may be outside the margin of resection



resection. Combining 5-ALA with brain mapping allows the most complete removal of tumor.

In addition to 5-ALA, advances such as intraoperative MRI, neuronavigation systems, and high-frequency ultrasonography are all used to improve extent of resection in patients with gliomas. Preoperative planning involves high-resolution MRI and often incorporates MR spectroscopy to identify regions of a glioma that may be of a higher grade.

Michael McDermott, MD was a fellow at UCSF from 1998-1990 (UCSF was the first medical school to offer a fellowship in neuro-oncology) before establishing a neuro-oncology program at the University of British Columbia, where he was also trained in skull base surgery. In 1992, he returned to UCSF to join the faculty and became director of clinical services and co-director of the radiosurgery program (together with radiation

oncologist Penny Sneed, MD). Today four radiosurgery systems are offered at UCSF, and the choice of which to use is tailored to each patient. These include Gamma Knife, CyberKnife, intensity modulated radiotherapy, and the TrueBeam linear accelerator. The Gamma Knife is especially effective in treating brain tumors and since it was adopted in 1991, close to 4000 patients have been treated with this modality.

McDermott also has extensive clinical experience treating meningiomas, and has led a series of retrospective outcome studies to refine existing treatment paradigms. One of these studies provides evidence for selecting out less aggressive meningiomas based on anatomic location. Patients with those types of tumors may benefit from subtotal resection to preserve function of critical structures, and any residual disease can be targeted with radiosurgery.



*Michael McDermott,
MD specializes in
surgery for gliomas,
meningiomas, acoustic
neuromas, and complex
skull base tumors*

The Brain Tumor Center also carries a great legacy in treating pituitary tumors. During his career, Charles Wilson performed over 3000 transsphenoidal operations for pituitary tumors, giving UCSF more experience with this delicate procedure than any other institution. Sandeep Kunwar, MD, who trained with Wilson, took over the practice in 2000 and was one of the first neurosurgeons to use the extended direct endonasal transsphenoidal approach to access challenging sellar tumors. Kunwar is one of the few surgeons in the nation whose practice is exclusively devoted to pituitary surgery. He has published some of the largest case series of transsphenoidal surgery for both adults and children in the world.

In 2007, neuroendocrinologist Lewis Blevins, MD was recruited from Vanderbilt University Medical Center to co-direct a new program devoted to pituitary

pathology—the California Center for Pituitary Disorders at UCSF. Like Kunwar, his practice is solely focused on the medical management of patients with pituitary disorders and together they provided comprehensive and highly experienced care to these patients. In 2008, they were joined by Manish Aghi, MD, PhD, who came to UCSF soon after completing residency at Massachusetts General Hospital and Harvard Medical School. In a five-year period (2007-2012), 1000 surgeries for pituitary disease were performed at the California Center for Pituitary Disorders.

Aghi's interests in endonasal surgery for pituitary tumors also extended into devising minimally invasive endonasal approaches for skull base lesions. With improvements in endoscopic technology, minimally invasive approaches can now be used to access tumors of the paranasal

Sandeep Kunwar, MD, Lewis Blevins, MD, and Manish Aghi, MD, PhD provide highly specialized care at the California Center for Pituitary Disorders at UCSF



sinuses and skull base. Many of these tumors were considered inoperable or were removed with wide, open craniotomies just a decade ago. Aghi and otolaryngologist Ivan El-Sayed, MD became co-directors of the new Minimally Invasive Skull Base Surgery Center in 2013 with the goal of offering safer surgeries to selected patients. Another goal of the Center was to pursue more effective treatment options in the laboratory. Working with Arnau Benet, MD in the Cerebrovascular and Skull Base Surgery lab, surgical

simulators and advanced 3-D neuroimaging are used for surgical planning, development of novel approaches, and optimization of current endoscopic routes.

In 2013, UCSF neurological surgery residency program alumnus Philip Theodosopoulos, MD returned from the University of Cincinnati where he had spent 10 years pioneering minimally invasive skull base surgery techniques. This expertise made him uniquely at home in the new Minimally Invasive Skull Base Surgery Center and today he is a leading figure in the movement away from invasive, open procedures towards treatment plans that combine smaller incisions, improved adjuvant therapies, new surgical technologies, and good clinical judgment that focuses on patient preferences and quality of life. Theodosopoulos is also a specialist in the treatment of acoustic neuromas, and has served as co-principal investigator for the largest prospective, multi-center trial of surgical treatment for these tumors.

Arnau Benet, MD (center) is the principal investigator of a cutting-edge, 3D surgical anatomy laboratory, where he works with otolaryngologist Ivan El-Sayed, MD (left) and neurosurgeon Manish Aghi, MD, PhD (right) to devise novel, safe endoscopic approaches to pathologies of the skull base through the endonasal corridor





*Neuro-oncologists
Susan Chang, MD,
Jennifer Clarke, MD,
MPH, and Nicholas
Butowski, MD*

Clinical Neuro-Oncology

Michael Prados, MD became chief of neuro-oncology in 1988 and shortly after became the leader of the NCI's North American Brain Tumor Consortium—a network of leading hospitals conducting clinical trials for adult patients with brain tumors. Working with him was Susan Chang, MD, who joined the BTRC in 1994, and was assistant director of neuro-oncology and director of clinical services.

Initially trials were focused on various types and combinations of chemotherapeutic drugs. In 1996, Gleevec became the first drug on the market designed to block protein kinases. Though it has not been shown to extend survival in brain tumors, many other tyrosine kinase inhibitors have since been developed and tested in brain tumors.

In 2002, the BTRC successfully

competed for one of the largest funding mechanisms offered by the NIH at the time, a National Cancer Institute Specialized Program in Research Excellence (SPORE) grant for brain tumor research. It has been continuously renewed through every funding cycle since that time, and several highly innovative projects and clinical trials have emerged as a result of the research. The BTRC has also been continuously funded by Program Project Grants (PPG), the first of which was awarded in 1973 and formed the basis for creating the BTRC. This highly competitive award funds tightly integrated projects performed by teams of investigators in synergistic research environments.

Critical to the success of both the PPG and the SPORE has been UCSF's neuroimaging group, led by Sarah Nelson, PhD.

The Division of Neuro-Oncology consistently receives the award for best outpatient care from the UCSF Medical Center



Neuroimaging specialists at UCSF have pioneered several advances in physiological and functional imaging that have allowed us to assess new biomarkers of response and progression. Neuroradiologist Soonmee Cha, MD has been another key collaborator in this area. Members of the neuro-oncology group are also recognized experts on the vexing topic of pseudoprogression, co-authoring the Response Assessment in Neuro-Oncology criteria for determining whether new enhancement seen on MRI after surgery is recurrence or an effect of therapy.

In 2005, several shifts occurred for the Neuro-Oncology Program. Prados became the director of the department's newly formed Translational Research Program, the goal of which was to more effectively move promising discoveries from the lab into

clinical trials by strengthening relationships with clinical trials consortia, government agencies, and industry. Chang became director of the Neuro-Oncology Division and Nicholas Butowski, MD, upon completing a fellowship under Chang and Prados, joined the faculty. By that time, the neuro-oncology group had become nationally recognized for its expertise in clinical trial design and published guidelines on reporting the results of phase I and II clinical trials of brain tumor therapies. Over 200 patients per year were being enrolled in studies at UCSF.

In 2008, Chang became the third faculty member to serve as president of the Society of Neuro-Oncology, which was founded in 1995 by Victor Levin, another UCSF faculty alumnus. She was preceded by Berger (1998-1999) and Prados (2004-2005). That same year, with the volume of

neuro-oncology patients from around the country continuing to climb, the Department hired Jennifer Clarke, MPH, MD, who had been a resident in the Department of Neurology at UCSF and a neuro-oncology fellow at Memorial-Sloan Kettering Cancer Center. In addition to conducting phase I and II clinical trials, Clarke has research interests in novel imaging methods of characterizing tumors and their response to treatment.

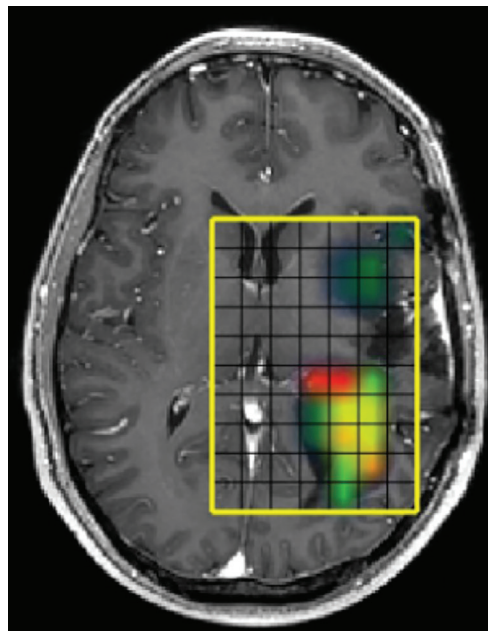
The NCI had funded several CNS consortia since 1993, and in 2009 it mandated a merge of the NABTC and the New Approaches to Brain Tumor Therapy Consortium (NABTT) to form the Adult Brain Tumor Consortium (ABTC). The ABTC is co-directed Prados and Stuart Grossman of Johns Hopkins University, and its primary objective is to perform phase I and II clinical trials across its 15 member sites.

Key to the development of new trials was biostatistician Kathleen Lamborn, PhD, who was a director of the UCSF Cancer Center Biostatistics Core before becoming a faculty member in the Department of Neurological Surgery. She provided statistical guidance for all clinical trials planned with the BTRC, but also for retrospective reviews based on the BTRC's clinical database, studies using animal models, and in vitro research. Today Annette Molinaro, PhD, recruited from Yale University in 2011, serves as director of the BTRC's Clinical and Biostatistics Core. Molinaro's

research interests are primarily focused on statistical genetics and computational biology, including prediction, survival analysis, classification, and causal inference with additional pursuits in cancer epidemiology and in the estimation of absolute risk in stratified case-cohort studies.

The most recent member of the Neuro-Oncology team is Jennie Taylor, MD who joined UCSF in 2014 after receiving an MPH from Harvard School of Public Health and completing the joint neuro-oncology fellowship at Massachusetts General Hospital and Dana-Farber Cancer Institute.

Today many of the clinical trials being developed within the BTRC revolve around the concept of personalized medicine. Following the sequencing of the genome in 2001, molecular profiling of tumors began and it became known that individual tumors of the same



Clinical research at UCSF funded by an NIH Program Project Grant uses metabolic imaging to uncover information on tumor burden and response to treatment

From left: Director of Neuro-Oncology Susan Chang, MD, Randi Murray, Margareta Page, MS, RN, Program Coordinator Idonah Molina, and Neuro-Oncology Social Worker Judy Patt-Smoker in a space dedicated for meeting with caregivers of patients with brain tumors as part of the Gordon Murray Neuro-Oncology Caregiver Program



pathological grade could have different mutations. Trials began that involved screening patients for specific mutations prior to giving them a drug that was designed to target that mutation. The Ben and Catherine Ivy Foundation sponsored a new consortium, led by Prados, in 2010 to specifically conduct trials in small, enriched populations of patients based on the molecular and genetic signatures of their tumors. Similarly, Prados and pediatric neuro-oncologist spearheaded the formation of the Pediatric Neuro-Oncology Consortium to conduct personalized medicine trials in children, discussed in this chapter under Pediatric Neurosurgery. Currently, 10 to 20 clinical trials for brain tumors are performed at one time at UCSF.

The California Institute for Regenerative Medicine (CIRM) awarded a grant of over \$19

million in 2009 to fund a multi-institution project to develop stem-cell-based strategies for treating glioblastoma. The studies were led by the UCSF Department of Neurological Surgery, with Berger serving as PI of the grant, and included collaborators at the Ludwig Institute for Cancer Research at the University of California, San Diego; the Burnham Institute for Medical Research; the University of California, Los Angeles; and the Salk Institute. The overall goal of the project was to genetically engineer stem cells that deliver therapeutic agents to selectively kill glioblastoma cells. The concept is based on the research team's discovery that stem cells naturally home to brain tumor cells.

In 2012, the Department competed for and won renewal of both the SPORE grant and the PPG grant, recognizing the

progress achieved through all previous cycles of these awards. Chang became the principal investigator of the PPG, taking the role over from Berger. The PPG continues to explore the integration of imaging and tissue correlates to optimize the management of gliomas. Results from the previous PPG identified physiological imaging parameters for characterizing newly diagnosed and post-treatment GBM, which could be linked to ex vivo metabolic profiles and histological characteristics. In the current research program, BTRC investigators are translating those findings into clinical use, as well as obtaining the first hyperpolarized carbon-13 metabolic imaging data from patients with brain tumors. This is a new technology that can be used to monitor pyruvate metabolism and may serve as a useful biomarker of drug delivery and response to therapy. The final goal of the PPG is to evaluate imaging and tissue parameters of newly diagnosed and post-treated GBM with specific emphasis on the genomic features of tumor heterogeneity and evolution.

The current SPORE program is the first brain tumor SPORE to include a project for pediatric brain tumors, focused on developing effective therapies for pediatric tumors with BRAF mutations. The remaining three projects of the SPORE program continue on the successes of the previous funding cycle: identifying genetic variations associated with increased survival in low-grade glioma; combining

genomic, physiological imaging, and histological data from low-grade gliomas to identify causes of malignant transformation; and improving immunotherapy for brain cancer by combining a heat shock protein vaccine with inhibitors of an aberrant cell-signaling pathway.

Another unique aspect of the current Neuro-Oncology Division is a program aimed at supporting family members, which was launched in 2013 and spearheaded by Susan Chang. The Gordon Murray Neuro-Oncology Caregiver Program was named in honor of Gordon Murray, who was treated at UCSF and lost his battle with brain cancer. Grateful for the state-of-the-art care he received, Mr. Murray's wife Randi Murray led a fundraising campaign to build a program that staffs a dedicated social worker to help families get the resources they need throughout the difficult experience of diagnosis, treatment, and bereavement.

Brain Tumor Research Center

In 2007, Dennis Deen, PhD retired as director of scientific research from the BTRC. He had been one of the earliest BTRC researchers, recruited from the University of Kansas by Ken Wheeler, and made significant contributions to our understanding of DNA damage and repair mechanisms. He also published some of the earlier research on the conversion

*Dennis Deen, PhD,
former Director of
Basic Science at
the Brain Tumor
Research Center*



of an oral prodrug called 5-fluorocytosine into the cytotoxic compound 5-fluorouracil. This treatment strategy is being used in current a clinical trial at UCSF that is combined with novel drug delivery strategies developed by Krystof Bankiewicz, Paul Larson, and Philip Starr. When Deen retired from UCSE, Russell Pieper took on the position of basic science director of the

BTRC, overseeing the operations of its laboratories and space.

As overall director of the BTRC, Berger brought dynamic growth and expansion of its programs and potential. The BTRC had great success in the areas of pharmacology, radiation biology, DNA damage, genomics, and experimental therapeutics. To that, Berger added new faculty to broaden the efforts in drug delivery technology, angiogenesis, stem-cell neurobiology, functional genomics, epigenetics, and immunotherapy.

During these years of expansion, the BTRC laboratories became dispersed across campuses. On June 2, 2009, the Helen Diller Family Cancer Research Building (part of the Helen Diller Family Comprehensive Cancer Center) opened on the Mission Bay campus, bringing all cancer research specialists (including all BTRC investigators) together under one roof. This shared physical space has been an important part of maintaining the collaborative spirit of the program.

*Brain Tumor
Research Center
investigators in 2013*



Today the BTRC is made up of over 20 laboratories with NIH research funding exceeding \$5 million per year. Broadly, the research being done can be grouped into:

Imaging of tumors

(Sarah Nelson, PhD, Tracy McKnight, MD, Soon-Mee Cha, MD, Sabrina Ronen, PhD)

These investigators use in vivo and ex vivo MRSI to help localize tumors for surgical resection as well as to non-invasively gain information about the tumor that might impact diagnosis as well as therapy. In the most recent iteration of the Department's Program Project Grant, they are the first group to be using hyperpolarized ^{13}C MRSI to monitor pyruvate metabolism as an early marker of drug action and response to therapy.

Drug delivery

(Krystof Bankiewicz, MD, PhD, Michael Oldham, PhD)

These investigators use convection-enhanced delivery and packaging of therapeutic agents into liposomes to improve local delivery of agents to gliomas. Nanoliposomal CPT-11 was developed through the UCSF Brain Tumor SPORE program and is currently being delivered via convection enhanced delivery in a phase I clinical trial for recurrent high-grade glioma.

Genomics

(Joseph Costello, PhD, Aaron Diaz, PhD)

These investigators use various CGH and array-based techniques to analyze the DNA and RNA of gliomas for alterations that may help in categorizing glioma or in understanding the underlying cause of the tumor. UCSF was one of four NIH Roadmap Epigenome Mapping Centers, directed by Joseph Costello, which contributed data to the national Roadmap Epigenomics Program.

Cell signaling/therapeutics

(Russ Pieper, PhD, William Weiss, MD, PhD, Jean Nakamura, MD, Theodore Nicolaides, MD)

This is the broadest of the research groups within the BTRC. This group includes animal models of glioma, investigations into the underlying disrupted pathways in glioma, and studies of the signaling pathways that effect conventional and targeted therapeutics.

Stem cell biology

(Arturo Alvarez-Buylla, PhD, David Rowitch, MD, PhD, Claudia Petritsch, PhD, Daniel Lim, MD, PhD)

This expanding group of investigators was the first to isolate human stem cells from the subventricular region of the human brain. Effort has now shifted to understanding how dysregulation

of these normal stem cells may contribute to glioma formation.

Angiogenesis/invasion
(Manish Aghi, MD, PhD,
Gabriele Bergers, PhD)

This group is focused on understanding how glioma develop the vasculature necessary for growth, how this process can be prevented, and how it may related to the ability of cells to migrate within the brain. Gabriele Bergers, PhD co-directs the Tumor Microenvironment Network (NIH U54) Grant with Valerie Weaver, PhD, professor in the Department of Surgery. The program funds three independent but interwoven projects that are supported by two scientific cores and one administrative core.

Tumor Immunology/vaccines
(Hideho Okada, MD, PhD)

This group is focused on understanding the ability of glioma to evade immune surveillance, and on modulation of pathways that might enhance the ability of glioma to be targeted by immune cells. From 2002 to 2013 the brain tumor immunotherapy program was led by Andrew Parsa, MD, PhD, who developed a heat shock protein vaccine for gliomas that is currently in a phase III, multi-institutional clinical trial. This work was developed in large part through the UCSF Brain Tumor SPORE and through collaboration with Russell Pieper, who helped identify a cell-signaling mechanism that could be blocked to enhance

the efficacy of the vaccine.

The immunotherapy program is currently led by Hideho Okada, MD, PhD, who joined the Department from the University of Pittsburgh, where he was involved with conducting one of the first immune gene therapy trials in patients with malignant glioma. He is currently involved in several lines of research, including a trial for chimeric antigen receptor T-cell therapy, which involves transducing a patient's own T-cells with an antigen receptor for a target glioma antibody. His group also identified factors necessary for T-cells to home to tumors in the central nervous system, and has developed clinical strategies to enhance T-cell homing.

Epidemiology
(Margaret Wrensch, PhD,
John Wiencke, PhD, Joseph
Wiemels, PhD, Kyle Walsh,
PhD, Shichun Zheng, PhD)

This group is focused on understanding the epidemiology of brain tumors. Their work includes identification of factors associated with glioma development and survival as well as identification of SNPs associated with increased incidence of brain tumors. Margaret Wrensch, PhD, co-director of the Division of Neuroepidemiology, is also a principal investigator of the San Francisco Bay Area Adult Glioma Study, which has extensively examined risk factors for glioma in the local population.

Patient Safety & Quality Improvement Program

Faculty

Catherine Lau, MD

In his role as chair, Mitchel Berger has devoted a great deal of time and energy to a topic that became important to him during his neurosurgical residency: patient safety and quality of care. Providing premier care was emphasized as the top objective from the beginning of his term as chair, but in 2011 the Department formalized the Quality and Safety Improvement Program, directed by Catherine Lau, MD, with goal of being a national leader in neurosurgical surgery quality and patient safety. The program is made up of a multidisciplinary team of faculty members, residents, nurse practitioners, physician assistants, clinic practice managers, nurses, pharmacists,

infection control specialists, and service line representatives. In 2012, the Department received the Healthgrades Neurosurgery Excellence award, which recognizes hospitals for superior patient safety outcomes in neurosurgery.

When Berger became president of the American Association of Neurological Surgeons in 2012, he took the opportunity to advance patient safety nationwide. The theme of the 2013 Annual Meeting of the AANS in New Orleans, Louisiana, was “Changing Our Culture to Advance Patient Safety.” Multiple leaders in patient safety and quality improvement served as keynote speakers, including Don Berwick, founder of the Institute for Healthcare Improvement, and Carolyn Clancy, Director of the Agency for Healthcare Research and Quality. Berger’s presidential address focused on the importance of patient safety and systems improvement, and



*Catherine Lau,
MD, Director of the
Neurosurgery Patient
Safety and Quality
Improvement Program*

urged neurosurgeons to embrace these principles as important pillars of their practice.

In keeping with the message given at the AANS, one of the first initiatives launched under the new program at home was to tackle the culture of safety in the operating room. The goals were to improve communication and instill a sense of personal responsibility among all members of the care team. An educational video on critical perioperative safety and debrief checklists was developed for surgical team members to review prior to and immediately after a surgical procedure. It has been viewed over 13,000 times on YouTube since it was uploaded in 2012.

As the program continued to grow, it focused on the four key areas of clinical effectiveness; clinical efficiencies; patient experience; and resident engagement. The department became the first in the nation to formally require quality improvement as a component of resident curriculum. All residents participate in core didactic lectures, perform self-guided online module learning, and obtain hands-on experience leading QI and patient safety projects through the UCSF Graduate Medical Education QI Incentive Project, in addition to a separate QI project of their choice.

In 2013, the Patient Safety and Quality Improvement Program was awarded a \$1.2 million grant from the UC Center for Health Quality and Innovation to develop and implement a clinical care pathway to improve and

standardize neurosurgery patient clinical outcomes and experiences at five UC Medical Center sites: San Francisco, Los Angeles, San Diego, Davis, and Irvine. Initiatives include standardizing postoperative debriefings amongst multidisciplinary care providers; introducing patient safety checklists to automate safety practices; designing more relevant patient education materials; and using validated questionnaires to measure safety attitudes among OR providers.

The Department of Neurological Surgery again received the Healthgrades Neurosurgery Excellence Award in 2013 and also became one of the first programs in the nation to submit data to the National Neurosurgery Quality and Outcomes Database. Sponsored by the AANS/ NeuroPoint Alliance, this was the first nationwide effort to collect data on safety, quality, and cost-effectiveness in the field of neurosurgery. The registry is web-based, and the first modules for data collection were for neurospinal procedures. UCSF spine surgeons presented on their prospectively collected data at the 2014 Annual Meeting of the AANS and showed that using the registry to identify patients who do not benefit from surgery will help to improve patient selection and surgical care delivery on a national level.



Mitchel Berger, MD gives the Presidential Address at the 81st Annual Meeting of the American Association of Neurological Surgeons

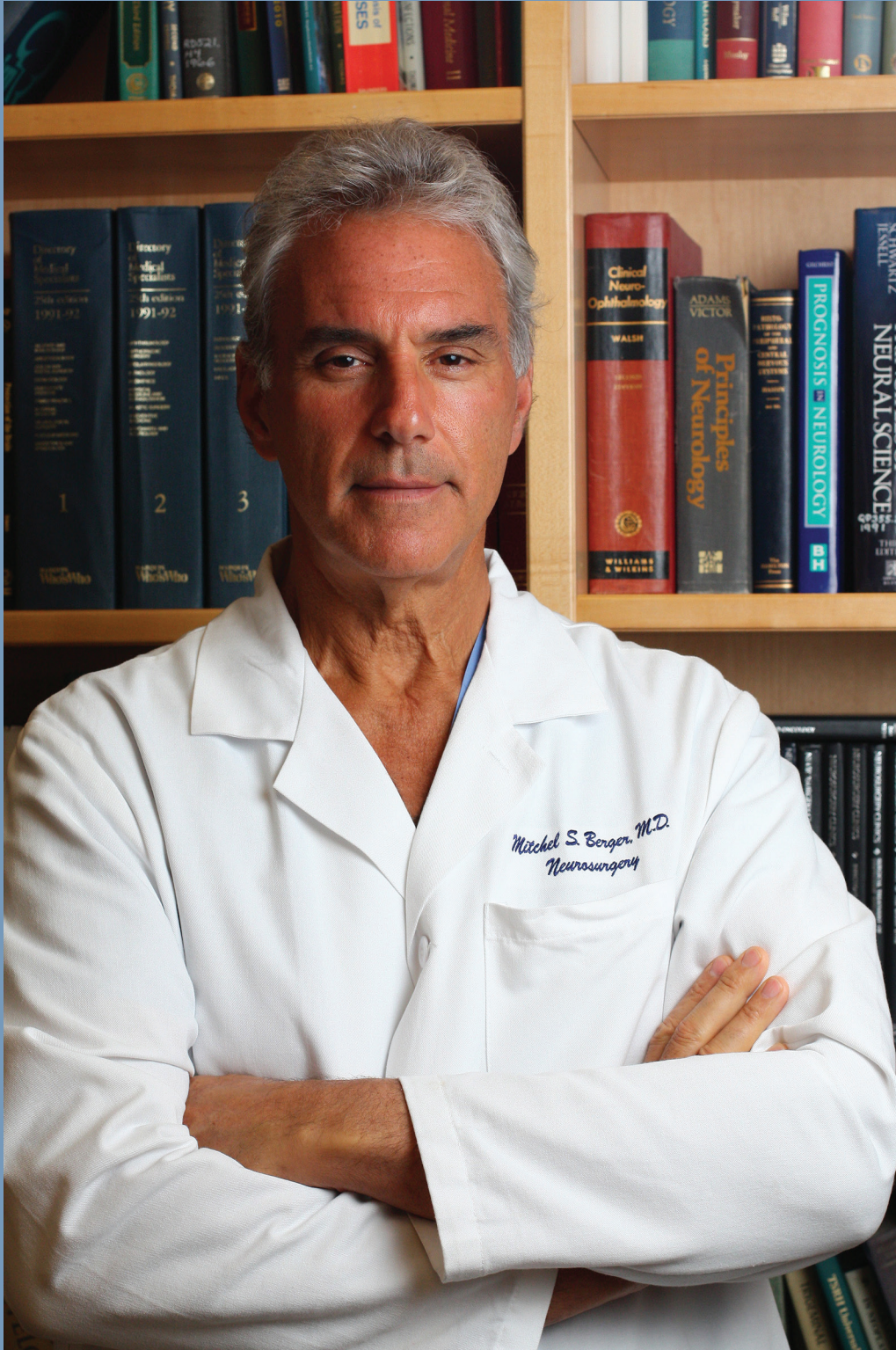
Chapter Seven

The Berger Interview Neurosurgery on the Frontier

“I wanted to create a department based on the two things that I felt meant not only the most to me but would be transformative for any department. And these two things had to do with the two principles of service and translation.”

In October 2014, Professor Dorothy Porter from the Division of History of Health Sciences at UCSF interviewed Mitchel Berger about returning to UCSF as chair of the Department of Neurological Surgery, his vision for cross-disciplinary collaboration and translational science, and his thoughts about the future of the department and the field. She began by following up on how he thought he could lead the department into a new era of strong clinical service supported by sustained basic science research.

BERGER: I thought I could do this here because this department had a history of providing neurosurgical service in all of its domains to the community. The community had always had a strength in academic neurosurgery at UCSF. It was always the go-to institution for tertiary and quaternary referrals—complex brain and spine cases.



So it had a precedent. But over the years, especially in the late 80s and 90s, it was eroded because of managed care and how practices were not allowed to send cases to us. And at this time there was a global awakening of neurosurgery to the point where there were developing areas of expertise not only in our own country but in other countries, which now basically prevented patients from leaving those countries. A number of circumstances and conditions began to erode the possibilities of receiving referrals and receiving patients at UCSF for critical care. But the reputation was once that UCSF was the beacon of care for complex neurosurgical cases and the question was how to get that back. The other issue had to do with the challenge of declining resources from NIH. I saw a de-emphasis on research, the research program was not being built up, and it was becoming left to a few basic scientists and they were becoming silos for survival. It was what I could call an R01-based research milieu. It wasn't team science. So the two things together started to look to me like there was potential because there was a history for team science here, but concerns over funding for scientists pushed them into two silos.

INTERVIEWER: Funding opportunities or funding initiatives started to shape the direction of growth and entire dynamic of a department that had been enjoying such success for so long by building collaborations. ...

BERGER: The department lost its incentive to be a specialist-type department. I saw a trend where neurosurgeons here were becoming more generalists.

INTERVIEWER: How did you anticipate that this might change? What were your strategic thoughts on how the department might flourish in the future based on its success in the past, and restore what had been eroded?

BERGER: Well I recognized my role as organizer of neurosurgery, which also led to me becoming president of the American Association of Neurological Surgeons. I started to see a trend in the 90s that most disciplines were becoming so complicated that it required and mandated subspecialization. Many departments were resisting it. And there was really no department that was based on subspecialization. A lot of that was because the faculty could not make a living through subspecialization, so those who wanted to do deep brain stimulation had to supplement their salary doing shunts and trauma. And that was not acceptable to the academic mission or to the eventual concept of translation. So I saw the writing on the wall. Basically, the way I tried to fix it was that I painted a picture here during my recruitment that I was very subspecialty oriented, that I was going to recruit a faculty that believed in subspecialization and also recognized the fact that certain surgeons are going to make more, income wise, than other surgeons. Because certain procedures pay more. The way we would even that out was to emphasize that the reason they came into academic medicine was to support their basic clinical or translational research program with funding that came from the clinical program. In other words, I had this philosophy that if you took someone and you just made them a spine surgeon I would not ask them to

also go do shunts and subdural hematomas, I would just send them to do spine, but in return they have to share their revenue stream with those who specialized in shunts or DBS, et cetera. So you had to buy into a philosophy and I was able to find people who bought into that philosophy. That is the substrate for the service component. Because when you are dedicated to a particular area, such as treating spinal disorders, then you can be more focused on delivering prompt, courteous, efficient service to patients.

INTERVIEWER: And does that also allow more time to divide time between clinical practice and research?

BERGER: If I made the subspecialists do other things, and if they knew that their income was linked to doing everything else, then the four hours that they might have on a given Thursday afternoon to write a paper or go to the lab would instead be spent doing a subdural hematoma to make revenue. So I eliminated that. I prevented cross-specialization.

INTERVIEWER: And was there an expectation when you started to recruit that they would be applying for research funding?

BERGER: I broke it down into three categories. Not only was subspecialization imperative and mandated, ... but there are three kinds of neurosurgeons. Those who are purely clinically active, who can write clinical research papers. That's a person who is 100% clinical. And then there is the neurosurgeon who is the hybrid, where they spend half their time in the clinic and half their time in the lab, and they are expected to be co-investigators on a grant, maybe a get a grant, bring in funding, and they have to write clinical as well as research papers. Then there is the person who is 75% or more committed to their research effort. Who can only spend one day a week in the operating room. And those are people who are encouraged to write their research protocols, and do clinical-based research on patients in the operating room. Or they can be purely in the laboratory.

INTERVIEWER: They can be engaged purely in bench science?

BERGER: Well they had to have some clinical effort, and then to that effort I paired everybody up with a scientist who I hired into the department, and then required that the scientist have a translational effort and that the clinician have a translational effort. So if the basic scientist wanted to work on worms or yeast, that was fine as long as they had some translational effort that resulted in some clinical-based publications.

INTERVIEWER: So as long as they are still researching the cure of some disease ...

BERGER: Right. And so that required a strategy, and the strategy was first to bring in a couple of people who are in that 100% clinical research domain who

would create a revenue stream for us, to develop seed monies for basic scientists. So we focused on clinical first and then worked to build the basic science program.

INTERVIEWER: Did you also encourage cross-departmental collaboration?

BERGER: Yes. Absolutely. There is great collaboration here at UCSF. I think one of things that attracted me here was the collaborative environment.

INTERVIEWER: Yes, Charlie Wilson talked about this in his interview with me a few years ago, and described what he admired in the academic liberalism of faculty here not being afraid to work outside their department or collaborate with others outside the boundaries of their discipline.

BERGER: I've never had anybody here, from Mike Bishop, to Elizabeth Blackburn, to Stan Prusiner, never had anybody refuse to take one of my residents, or to collaborate with us on any clinically relevant projects. I have collaborated with all three of them. And there's three Nobel laureates.

INTERVIEWER: And you wouldn't find that at every university! How successful has your overall strategy been as far as what you wanted to achieve?

BERGER: It's exceeded my expectations, and there are a couple of different ways to measure that. One is to look at national parameters, how peers judge you. A recent poll rated us the number one residency program in the country for instance, so we have these metrics, and then we have other metrics in terms of growth. Patient volume, number of operative cases, number of clinic cases, number of staff we have hired, number of faculty we have hired, expansion of the residency training program.

INTERVIEWER: Can I ask you about some of the revolutions and developments in the life sciences and in medicine and how you think it is affecting current clinical practice and what do you think we might see in the next 25 years? I'm thinking of genomics ...

BERGER: I think the genomic era – but it would be short-sighted to just leave it at that because I think perhaps the biggest revolution that has impacted us is imaging. What's happening in imaging has been dramatic. Not just in anatomical imaging, but in physiological imaging, showing us function in the brain and spinal cord, metabolic imaging, showing us how cells process information, how they utilize drugs we use. The imaging piece has revolutionized our ability to formulate strategies for surgery, and to implement strategies for surgery. All of our imaging is used in navigation systems in the operating room. We navigate in all surgeries based upon preoperative imaging. We have intraoperative imaging now in the form of CT or MR that help us to make decisions during the course of surgery ... so imaging is probably the biggest thing to impact neurosurgery during the course of surgery. Then you have all the technical advances, mean-

ing all the advances in the biomaterials, that have enabled us to develop better instrumentation, better drill systems, stronger aneurysm clips, these are huge advances. Then you have the genomic revolution, which has enhanced our ability to understand disease processes. We have been given huge amounts of information that gave us new targets, but in the first ten years of having this information we didn't have the therapeutics, so now I think we are trying to catch up.

“That is how this field is going to evolve. In terms of restorative therapy, in terms of personalized therapy, and in how we are going to harness technology, and biomaterials, and imaging, and genomics to make that landscape appear before our eyes. All in the course of translating what we do with our basic science partners to continue to provide outstanding service.”

INTERVIEWER: So do you think that personalized medicine is a reality?

BERGER: It is. And in fact, historically speaking, this week we actually did our first case of personalized medicine in neuro-oncology here at UCSF — and this is through a consortium funded by a private group called the Ivy Foundation. What this means is that for the first time in our history we were able to take a patient and the tumor that was taken out is now, literally within 72 hours, being deep sequenced so we can find the four most common mutations seen in that person's tumor and based upon all the therapeutics that we have available to us will now target those mutant pathways to try and block the aberrantly expressed proteins.

But whatever the future prospects, this department can proudly reflect on the history of its own innovations and achievements. To highlight a few:

- Philip Starr and Paul Larson developed a better way to put deep brain stimulating electrodes into MRI using the ClearPoint device.
- Chris Ames has figured out ways to reconstruct the spine to help overcome degenerative scoliosis and devices to help people walk upright again
- Paul Larson discovered a new strategy to treat tinnitus using deep brain stimulation
- Neuro-oncology developed personalized approaches to therapy for brain tumors
- Manish Aghi and Phil Theodosopoulos have harnessed the power of endoscopes to approach previously unapproachable regions of the brain or skull base

- Mike Lawton developed strategies to operate in areas such as the brainstem to remove vascular malformations or to take vessels from different parts of the body to bypass deficient vascular areas to augment blood flow to prevent strokes or remove blood vessels that are diseased causing a stroke
- Geoff Manley has rewritten the book using imaging and biomarkers to define the course of traumatic brain injury

“These are the frontiers,” says Berger. “All of which speak to the role of sub-specialization in allowing us to translate because we are not defocused, we are focused. And that has to be the theme of the future. We are at the frontiers of many things.”