Max Fink: *An Experimentalist's Journey in Neurology and Psychiatry: 60 Years in Clinical Neuroscience*

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The ultimate court of appeal is observation and experiment, and not authority.

Thomas H. Huxley [1]

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01 Starting Out

I came of age in America during the war years of the 1940s and 1950s,and for six decades have been atreating clinician and researchercaring for neurologic and psychiatric ill. For many decades, the mentally ill had been warehoused in large sanitaria far from city centers, at least until the seizure therapies, electroshock and insulin coma, were introduced in the 1930s +slowing the growth of mental hospital populations from the peak in 1955 at 560,000 patient beds in the United States. The efficacy and the mystery of these treatments, inducing grand mal seizures, became my lifelong challenge. The treatment methods, however, were highly controversial in the public and within the profession. For my interest I was often berated and have thought that a less hostile life might have been preferred.

The 1950s and 1960salso brought new psychoactive medicinesthat changedbrain chemistry and physiology allowingtens of thousands of the severe psychiatric ill to leave U.S. hospitals and live at home, or on the streets, in jails, in flophouses, or in and out of community hospitals. By 2010 the number of accredited psychiatric hospital beds had fallen to 43,000. Identifying the benefits and developing treatment protocols for these new medicines became a professional challenge. As the effectsof the new agents were measurable in the electrical readings of the scalp recordedelectroencephalogram (EEG) patterns, and the digital computer revolution offered means to quantify these effects, the new science of pharmaco-EEG occupied 35 years of my research life.

My interest in the effects of psychoactive medications on the human brain included active studies of the opioids and cannabis that were interdicted by governments as addicting and life-threatening. In my later years I actively led aneffort to rescue the disorder ofcatatonia from its entombment within the poorly understood concept of schizophreniaand show that it was an independent, identifiable, verifiable, and treatable syndrome. Bringing it out of its closet encouraged worldwide recognition. Catatonia is unique among the behavior disorders in having two effective treatments and a useful verification test, which makeseach recognition of the syndrome life-saving.

The arc of my professional career runs from a childhood in the Bronx, medical school in New York City, a decadeorganizing Hillside Hospital’s research facilities, a brief stint as an Psychiatric Institute head in Missouri, back to New York for a continuing academic career in different hospitals, spending35 years teaching psychiatry at the State University of Stony Brook.

After meeting requirements for professional certification in neurology, psychiatry, and psychoanalysis, I spent my years as an experimentalist researcher and teacher.

Beginnings

I began my medical school trainingin 1942,an optimistic time for students of neurology and psychiatry. New tools imagedthe brain and its blood vessels andrecorded the brain's electrical activitygiving more accurate pictures of the brain's functions. The epilepsies were tamed by phenytoin and barbiturates. Antisepsis, local and systemic anesthetics, and improved surgical skills assured safer brain surgery. The drastic treatments of malarial fevers and arsenicals gave some relief for neurosyphilis, but by the end of the war penicillinwas recognized as a specific treatment for this dread disease, relieving the ill and liberating social andsexual behaviors by reducing the fear of venereal disease. Repeated inductions of grand mal seizures by insulin, Metrazol, and electricity decreased the agitation of manic-depression and the psychoses, halting the exponential rise in the numbers of hospitalized chronic illthat marked the first decades of the 20th Century.

An enthusiasm for Freudian psychoanalysis enticedphysicians and psychologists to open offices and clinics for the care of the emotionally wounded. Even before the early successes of psychotropic drugs, the pessimism of the asylum was breached and psychiatry had become a favored medical specialty. Of the graduates of my medical school class in 1945, more than 10% opted for advanced training in psychiatry, and a fewlike me trained in both neurology and psychiatry.

The opportunity to become an experimentalist was encouraged by the war. By my second medical school year the leading teachers at the New York University Medical School were in military service, staffing a major overseas hospital center. Much patient care fell to the students, who were expected to draw blood and spinal fluid, test experimental medicines,and learnsurgical techniques. We cared for patients with minimal supervision. During residency training in the immediate post-war years, returning veteran teachers, imbued with the excitement and enthusiasms of experiments encouraged during the war, testednew medicines and new methods with minimal attention to patient consent that are core questions in the today's medical care and study.

Marriage and Personal Life

When I returned from a trip as the ship's surgeon on the Grace Line's *Santa Monica* in March 1948, I was introduced to Martha Pearl Gross, a student at Barnard College who was dockside awaiting her parents. I was then a resident at Montefiore Hospital and I visited her parents in Great Neck and courted her. We married a year later, on September 11, 1949.[1]

I continued my resident training in neurology and psychiatry residency years at Bellevue and then at Hillside Hospital. Late in 1952, Hillside Hospital's Medical Director, Joseph S. A. Miller, asked me to supervise the ECT/ICT service on a half-time basis. I happily accepted as it offered an assured salary while I built up a community clinical practice.[2] Two general medical hospitals opened: Long Island Jewish Hospital on the grounds of Hillside Hospital and the North Shore Hospital in Manhasset a few miles nearby. I was appointed to the Neurology services of both hospitals, and organized their EEG Departments. My community practice blossomed, reports of the Hillside studies I had conducted were being published and presented at national and international meetings. Our family grew with our son Jonathan born in May 1951, and daughters Rachel in 1956 and Linda in1958.An offer of a full-time appointment to Hillside at double my salary in the spring of 1958 was so enticing that within six months I had closed my office, resigned from the staffs of other hospitals, and began the life of a full-time academic.[3]In 1962 I moved to St Louis to head a research institute, returned to New York in 1966 to join the faculty of the New York Medical College, then taught at Stony Brook University in 1973, until my retirement in 2005.

Peregrinations

In 1962, I was invited to direct a new research institute, the Missouri Institute of Psychiatry on the grounds of the St. Louis State Hospital, with the academic affiliation as Research Professor with Washington University School of Medicine. We found a home in the Lake Forest suburb, and our children were soon registered in their schools. When our youngest child, Linda was schooled daily, Martha enrolled at Washington University for an M.A. in Education, which led to her lifelong elementary school teaching career.

We adjusted to a new community even though warnings of religious intolerance appeared early. When we were looking for a home, I asked George Ulett, the head of the State mental health services who had invited me, where he lived. "In Ladue," continuing with the advice,

"You would not be happy there." I did not catch the warning but we soon experienced the strong smells of anti-semitism and nativism that pervaded the St. Louis communities, the state, and even the hospital government during our stay. My appointment to the MIP was announced as "Austrian Heads Institute."

Two years later the Missouri State legislature failed to renew the biennium funding for the Institute, and I and the other scientists fled. I found a position at the New York Medical College to lead the opioid detoxification center at New York City's Metropolitan Hospital beginning in July 1966. Martha and I found a home in Great Neck and enrolled our children in the community schools. Martha began teaching students at the elementary schoolin Port Washington and then the Great Neck schools. I set up my computer center to analyze EEG at the Psychiatry Department offices on East 102nd Street, developed an ECT study at Gracie Square Hospital, and obtained a Federal contract to study the systemic effects of hashish in users in Athens, Greece.[4] I had remarkable students in Richard Abrams, Michael Taylor, and Robert Levine and was fortunate in the collaboration of Rhea Dornbush, Jan Volavka, and Donald Shapiro.

In July 1969 Herman Denber, the director of psychiatric research at Manhattan State Hospital, invited me to join him on a single-engine Cessna 172 flight that he piloted over the Hudson Valley and the New York harbor. It was a day of brilliant sunshine and I decided to learn to pilot a small plane. A flying school was still active at LaGuardia Airport and I began my flying lessons on July 4, 1969. I soloed Nov 13, 1969. For the next few years I leased airplanes at Long Island's Republic and Westchester airports. I piloted Jonathan's move to Colby College in Maine and flew to professional meetings. A transcontinental trip in May 1970 from Westchester Airport, through Tulsa, then the next day on the southern route to San Diego and San Francisco with Herman Denber to attend the APA meetings.[5] Interested in leasing a summer home in the Adirondacks in May 1972 Martha and our daughters flew to Lake Placid. My last flights were in June 1973.

In 1972 a new medical school was established 40 miles East of Great Neck at Stony Brook, Long Island. Chairman of Psychiatry Stanley Yolles invited me to join his faculty to lead research in psychopharmacology and ECT. I gladly accepted to avoid the hassles of travel toNew York City and the social and political hostilities of the addiction community and the city leaders. For the first few years I taught students and residents at the Central Islip Psychiatric

Center and the Veteran's Hospital in Northport. With the opening of University Hospital in 1980 I organized my teaching and my EEG and ECT studies at that facility.

Martha and I bought a home on the Stony Brook harbor in 1980. By that time our children had each graduated with doctoral degrees in the sciences and had begun their academic careers.[6] Jonathan's degree from Stanford University led to a post-doc in volcanology and an academic career at Arizona State University in Tempe. Rachel graduated from Cornell and Duke Universities in marine biology and began teaching at Mt Holyoke College in Massachusetts. Linda received her degrees from Amherst College, among the first women after the college became co-ed, and her doctorate in entomology at University of Florida in Gainesville and began a teaching career at Sweet Briar College in Virginia. Each married at our Nissequogue home and soon the family grew with four grandchildren.[7]

My research work was well supported by NIMH and private foundations and I led a consortium to study continuation treatments after successful ECT in depressed patients. For various administrative reasons I was unable to carry out my portion of an NIMH funded collaborative study at Stony Brook and I moved the project to Hillside Hospital, a return for me after 35 years. For the next decade I supervised this study, developed others, and continued teaching.

In 2005, at the age of 82, I left the study group at Hillside and retired to my home in Nissequogue to pursue writing projects. Since 1999 I have been writing articles and books with Michael Taylor, Jan-Otto Ottosson, Edward Shorter, and multiple colleagues on convulsive therapy, catatonia, ethics, and melancholia. I also continued to lecture and attend national and international meetings until 2015.

Martha died suddenly on March 31, 2016 and since then I have remained at my home spending my time writing.

What follows charts the course of my research and thinking about mental illness over six decades. The central issues are the relief of neurologic and psychiatric illnesses, patient care with controversies over electroshock, psychoactive drugs, catatonia, and melancholia.

Stony Brook Library Archives

When Edward Shorter and David Healy visited my home in 2006 to examine my records for their book on the history of the shock therapies, they were impressed by the extent of the files

and asked what I planned to do with them. They encouraged their being publicly archived. The Stony Brook University Library archivist Kristen Nyitray examined and agreed to archive the collection.[8]

02 Schooling

I was born in Vienna on January 16, 1923, the same year that my father Julius Fink graduated from the University of Vienna Medical School. He had special training in the new science of radiology and took an externeship in medicine and radiology at the Bergen County Hospital in New Jersey.

My mother Broniaslawa Lowenthal (*Bronia*, *Bronka*) had been a medical student at the University of Vienna, one of very few women admitted. She was much courted and married Julius on March 12, 1922, in her third year of training. Within a year I was born. My mother cared for me in Vienna while my father worked in New Jersey. My mother and I sailed from Bremen on the SS George Washington on October 17, 1924 arriving in New York on October 24, shepherded under the watchful eye of her younger brother Adolf, who had been sent by the family from New York.

In our family setting, I always "knew" that I would become a physician. Admission to medical school in the US was under small quotas for Jews, and to successfully gain admission one needed to be "in the top of the class." My elementary and high school classes were at PS 77 and James Monroe High School in the Bronx, a few streets from my father's office at 1201 Elder Avenue. My high school teachers, sympathetic to my goal and recognizing the problems in college and medical school admission, encouraged me to be a leader of the Arista Club, to publish articles in the the German-language magazine *Plaudermäulchen,* and to be the Manager of the football team, gaining my athletic "M" at graduation.

I graduated from high school in January 1939 at age 16 and enrolled at the New York University College campus at University Heights of the Bronx for its Feb/Sep program. In 1942, at age 19, I began medical school at NYU School of Medicine. The demands of WW II collapsed our training period to 3 years, and I graduated on June 12, 1945 at age 22, the youngest member of my class.

My medical experience began in my father's office, developing x-ray films, clinical laboratory tests, and answering the telephone when he was out of his office. He was a general medical practitioner in a free-standing office equipped for clinical laboratory tests of blood and urine, x-ray and fluoroscopy, and electrocardiography. He trudged to house-calls at all hours of day or night, in all weathers. He was a model for my brother and myself, both selecting medical careers.

My schooling emphasized an experimental, "hands-on" approach beginning in college where teachers answered questions by suggesting experiments. When I entered my junior college class, I volunteered for the project to count the numbers of mitoses in the neural ependymal layer of the 48-72 hour developing chick, to answer the question how the diurnal light-dark cycle impacted the growth rate.[1] Other students had been asked to measure the rates in the 24 to 48 and 72 to 96 hour cycles. (As I recall, the light cycle did not affect the rates of mitoses.)

Medical School

My letter of admission to New York University College of Medicine arrived on December 6, 1941, the day before the Japanese attack on Pearl Harbor and the entry of the nation into war. That Sunday I was accompanying my father on a house call, listening to radio news, when the attack was announced. My parents had actively encouraged the emigration of friends and classmates from Vienna, acting as surety for their transitions to America. They had avidly followed the news of the war in Europe and were particularly agitated by the Nazi murders of Jews.

I began a three-year intensive medical school training program at New York City's Bellevue Hospital in June 1942. We were sent to Fort Dix in New Jersey for a week's military orientation and returned to classes as soldiers in the U.S. Army.[2] The war had called many experienced faculty members to military duty offering the students unusual opportunities for hands-on medical experiences and responsibility for medical and surgical procedures far beyond our knowledge and experience.

I vaguely remember the anatomy and chemistry lessons of the first year. The cadaver was an elderly, skinny woman. My teammates were Felix Wroblewski, who later joined the Rockefeller Institute and Luther Cloud, an officer in an insurance firm. Neuroanatomy was taught by Wendell Krieg, who asked each student to make paper mache crossections of the human brain. These models were supplemented by brain slices preserved in formaldehyde in crocks that allowed us to map the brain's nuclei.

Neurosyphilis. Clinical teaching began in the second year and in an assignment to the syphilis clinics I was taught by Bernhard Dattner, a 1938 émigré from Vienna. He had studied under Julius Wagner-Jauregg, the 1927 Nobel Prize winner in Medicine for his report that

malaria induced fevers relieved one third of patients with active neurosyphilis.[3] While at Vienna's Allgemeines Krankenhaus, Dattner had reported that the number of white cells and levels of protein in the cerebrospinal fluid (CSF) were highest in the actively ill, making CSF examination indices of the severity of the illness and as guides to treatment.[4]

Withdrawal of cerebrospinal fluid by lumbar punctures, usually between L3 and L4 vertebrae, are often followed by severe headache. To reduce this incidence Dattner obtained the CSF from the 4th ventricle by an occipital puncture to the cisterna magna.When I came to the clinic, Dattner demonstrated the technique and for the next month I was responsible for monitoring the progress of the patients by repeated ventricular taps. I was taught this technique and assumed that it was a customary procedure, despite the risk of penetrating ("pithing") the brain stem. The procedure, as I learned later, is now considered too riskful to be considered even by experienced neurologists and neurosurgeons.[5]

But neurosyphilis is a late development in the life course of syphilis, appearing years after the original infection. The symptoms develop slowly, making difficult an accurate diagnosis with its devastating consequences in personal life and the risks of the toxic treatments. A principal sign of the disease is pupillary irregularity and failure to narrow with a light stimulus (the Argyll-Robertson pupil). When mental and neurologic symptoms appear, this sign is present in less than 60% of known ill. Dattner argued that tests of the CSF offered better and more reliable criteria of the severity of the disease. The presence of cells, elevated protein and positive colloidal gold reaction tests were the guide to fever treatments. The CSF changes normalized in the patients who responded to the fever therapies.[6]

While syphilitic patients were treated with arsenical preparations, the more actively ill were also subjected to malarial or “sweat box” fevers. Patients remained seated for hours in a box heated by lightbulbs with only their heads exposed. The treatments were severely debilitating and assuring hydration and monitoring body temperatures was one of my responsibilities. Follow-up studies did show improvements in serological and CSF tests and some relief in psychiatric symptoms. I was astonished by what patients were willing to suffer on the promise of cure.[7]

During my schooling in 1943, Bellevue Hospital’s R-S buildings were filled with more than 200 patients with syphilitic disorders. Six years later in 1949 when I returned as a resident

in neurology, 2/3 the beds no longer served these disorders, the remarkable impact of penicillin therapy.

In later years, when I applied novel treatments for psychiatric ill, I sought similar test guides to treatment outcomes – as in the Face-Hand Test, the amobarbital denial test, and the high levels of slow wave and spike activity in the interseizure EEG as measures of progress in ECT. Later I was fascinated by dexamethasone suppression tests in melancholia and the lorazepam response test in catatonia.

Pharmacology. Student training in pharmacology included individual experiences with medications administered to and by fellow students – morphine, scopolamine, atropine, vasodilators, nitrous oxide, amobarbital, and amphetamine are those that I recall. Doses were pharmacologically active and our observations were recorded. Blood samples were taken and nasogastric tubes passed. The hilarity induced by nitrous oxide inhalation and the pleasant feelings associated with barbiturates made some of us look forward to these classes. For others, the unpleasant experiences with scopolamine and morphine drove them from the laboratory.[8]

Osteomyelitis. Among children, infections of fractured bones required intensive care. Débridement (surgically removing dead and infected tissues) was followed by repeated flushing with warm saline and dressings to keep the wounds clean to encourage healing. Plaster casts restrained the movement of limbs. In my junior year during my rotation in pediatric surgery I debrided children's wounds. An ongoing research study applied live maggots to the open wound to clear the pus and dead tissues. I cleansed wounds of bone fragments and tissue debris, washed out wounds with sterile saline solutions, created a plaster protective shell to immobilize the limb, and applied live maggots for days at a time. Surprisingly, the treatments were effective, allowing surgical repair of the skin and bone. This usage disappeared with the introduction of antibiotics but references now appear from time to time citing maggot therapy in resistant infections.[9]

Barbiturates. During a rotation on the active psychiatric service at Bellevue Psychiatric Hospital in my senior year I was taught to use amobarbital (Amytal Sodium) to control agitated and aggressive behaviors. It was also used to relieve catatonic refusal of food, mutism, and posturing. I do not recall the use in stuporous catatonic patients, a use that became important to me four decades later.[10]

Internship: My first Random Controlled Trial

My medical internship continued the same 'hands-on' experiences. During a rotation on the pulmonary medicine service, patients with pleural cavity infections (empyema) filled the beds. Every other day we introduced a large 18-guage trocar between the ribs into the pleural space, removed pus, and washed out the pleural space with warm saline. An ongoing experiment washed the pleural space with either sulfadiazine or an experimental substance "x," with each patient randomly assigned by the odd or even final number of their chart record. Supplies of "x" were locked in the safe in the hospital director's office. As samples were withdrawn, the amounts were carefully recorded according to the patient's chart number. Within a few weeks the superiority of substance "x" was apparent, even to a neophyte physician – the pleural fluid thinned rapidly from yellow putrescent pus to pink serous to clear fluid; fever curves flattened, pain and apathy disappeared, and appetite and activity improved, all within 10 days of administration.

A young febrile woman with empyema was admitted with her nursing infant. The medication assignment was for the sulfonamide. Assuring myself of the ethics of the switch for a nursing mother, I administered "compound x" and did so daily. When the empyema rapidly cleared, the Attending physician Dr. Eli Rubin was puzzled. Checking the records he noted the switch and in anger, marched me to the Medical Director's office and asked for my suspension from the internship. I had broken two rules, direct orders of an Attending physician and the research protocol. When cooler heads prevailed a few days later I was re-instated but the lesson of adherence to research assignment was learned. (Compound "x" was penicillin.[11])

It was my first experience with a random controlled trial, the comparison of a new treatment to an old.

Work schedules were exhausting, with 48 hours on call frequent; learning from an Attending physicians who supervised each patient's care was payment for the exhausting hours. The neurologist Nathan Savitsky visited his patients at 7:30 each morning, inviting any interne to join. He was a dynamic and knowledgeable teacher, citing the literature much as Google or Wikipedia do today. I joined him often and soon I was called to attend the autopsies of patients we had examined together. The logic of diagnosing pathology by the symptoms and course of illness and the demonstrated neuropathology was impressive.

During schooling I lived at home in the Bronx, about an hour's subway trip. Although school began at 0900, the Army rules insisted that we be present for roll call each morning at 0730. Such was not easy during the winter and I soon was reprimanded for lateness and ordered to guard duty as punishment many Friday evenings.[12]

We had some holiday time and on June 6, 1944 – D-Day - I and fellow classmates were camping on Big Burnt Island in Lake George to hear the shouts and waving paddles announcing D-Day as classmates canoedback from Lake George Village.

Military career and travels as ship's surgeon

Active military duty began in April 1946. After two weeks of field training I was assigned to a regimental field station in Camp Campbell, Kentucky, managing morning sick-call and incidental accidents and injuries.[13] That winter I received orders to attend the Army School of Military Neuropsychiatry at Fort Sam Houston in Texas for a 4-month intensive program in neurological and psychiatric examinations, management of traumatic injuries and combat stress reactions, psychodynamic principles, and lectures on ECT, insulin coma, and lobotomy. Many instructors were imbued with the fervor of psychoanalysis, promising cures for the most severe mental disorders. We were enthralled and so enthused that many of us sought psychoanalytic training when we returned to civilian life.[14]

After completing the course I was assigned to the Fort Knox Station Hospital as Chief of Psychiatry. Three wards of 30 patients each included a range of severely ill psychotic patients, some undergoing insulin coma and some ECT. The nurses and technicians were competent and experienced, more so than I, and my responsibilities of supervision were light. The nearest medical school was in Louisville, about an hour away. I attended weekly Grand Rounds in Neurology with Ephraim Roseman and took a course in the Rorschach test procedures with Arthur Benton.[15]

The war against Japan ended with the atomic bomb in August 1945, saving the lives of many thousands of American soldiers as well as of many Japanese. By 1946 President Truman, faced with the costs of a very large active military service, ordered the summary discharge of thousands of soldiers on duty. Among my military assignments was as a member of an Officer's Board to decide on the qualifications for soldiers desiring to remain in the post-war career Army. As the panel psychiatrist I used the Rorschach Test in the recommendation for discharge or

retention. My comments had little influence on the Boards' decisions, as only the longest serving and well merit awarded soldiers were recommended for retention. At the end of November 1947 my service was suddenly ended after 20 months active duty.[16]

I had enrolled for residency training in neuropsychiatry at the Montefiore Hospital with H. Houston Merritt for July 1948. The tantalizing question became whether to advance my medical training experience to January or to spend the six-month gift of freedom elsewhere. After continuing years of schooling and military service the glamour and challenge of a position as ship's surgeon led me to Grace Line's Hudson River Pier 57.[17] A position was open on the *S.S. Santa Maria*, a C-2 freighter with 52 passengers, leaving five days later to the west coast of South America, with stops at ports in Columbia[18], Peru[19], and Chile.[20] The duties of the ship's surgeon were sick call sessions twice a day, writing health status reports of passengers and crew on entry to ports, examination of food storage areas and freezers for vermin, and accompanying health inspectors as they surveyed the ship in each port.

It was possible to visit the port cities during one to two days of loading and unloading cargo. I visited the local mental hospital in Lima where Honoria Delgado cared for the severe mentally ill. He encouraged patient art. Although the hospital was more like a prison with stone palettes, iron rings in the walls to attach restraints, the drawings and paintings adorned the walls of the wards. These paintings were foreeunners of enthusiasms for "Outsider Art" in the 1970s.

After two 5-week voyages to Valparaiso, I signed on the *Santa Monica* for a 3-week cruise to Cartajena and Barranquilla on the north coast of Colombia.[21] My final trip was on the American Export Lines *Marine Perch*, a large C-4 passenger ship that served as troop carrier during the war and as refugee ship after the war. We travelled to Palermo (Sicily), Naples (Italy), and Valleta (Malta). The ship had a large medical complement and the work was easy.

After landing in Naples, I hired a taxi for a 28-hour trip to tour Rome visiting the Roman ruins during the night. When we landed in Malta, I visited the port and soon I had a following of young boys and girls, pointing to my white uniform and especially my white shoes. When I enquired as the cause of the hilarity at a silver shop managed by a Jewish owner he pointed to the almost universal black clothes of women and men, honoring the dead. "I must be rich, very rich, to wear white shoes."

Neuropsychiatry Training at Montefiore and Bellevue Hospitals

As the new hire at Montefiore Hospital's residency in July 1948, I was first assigned to the neurosurgery rotation. As a student assistant during brain surgery with Dr. Leo Davidoff, the hours standing as a masked assistant in one place without voice or movement were enervating, and I escaped to the clinic as quickly as I could. Percutaneous carotid angiography had just been perfected and the neurosurgical residents taught me how to insert the needle into the carotid artery by touch, rapidly inject radio-opaque dye, and call for three x-ray images at 2-second intervals.[22] I became skilled in identifying the signs of meningioma, glioblastoma, subdural hematoma, arterial aneurysm, and arterial blockage.

In pneumoencephalography air is injected into the cerebrospinal canal and ventricles through a needle puncture between lumbar vertebrae 4 and 5. The air fills the ventricles outlining the spaces showing abnormal images. I became skilled in obtaining cerebrospinal fluid and used the technique in later studies.[23] The films showed tumors, bleedings, and encephalopathies, directing neurosurgical intervention when appropriate.

Montefiore Hospital was a museum of chronic neurological disorders that had been under study for decades. The film library included examples of classic syndromes of abnormal motor movements and seizures that I studied to properly label the peculiar movements. I have no recollection of experience with psychiatric patients.

In July 1949 I continued training at Bellevue Hospital, first as resident in neurology and then in psychiatry. Percutaneous carotid angiography had not been introduced to the hospital so I brought this new technique to the Neurology Service. After obtaining permission from Prof E. D. Friedman to develop such tests, a fellow resident Joseph Stein[24] and I built a film holder for multiple images and collaborated with radiologists to organize a service. The first films of a subdural hematoma showed the blood vessels, displaced by a dark mass, clearly outlining the lesion and its effects, encouraging surgical relief. Over the next year, we did 102 procedures, reporting a high diagnostic success rate and a 5% morbidity rate.[25] Studies of the CSF showed no persistent abnormalities as a result of these tests.[26]

After one such procedure, a young man was lying in bed, alert and relaxed, staring into space. Asked what he was seeing and pointing to objects in the room, he pleasantly confabulated responses of things he did not see. He had developed an acute syndrome of visual neglect and denial of blindness known as the Anton Syndrome.[27] After a few days of nursing care his

condition resolved. My teachers interpreted the phenomenon as an interaction between the physical changes induced by the injection and the psychological "defense mechanism of denial" based on psychoanalytic philosophy.[28] It was a lesson in applied psychodynamic philosopy to psychopathology.

Other clinical experiences were as intriguing. The folk singer Lead Belly -- Huddie Ledbetter -- was admitted with advanced amyotrophic lateral sclerosis. No effective treatment was known but many thought the disease resulted from neurotoxicity caused by the passage of toxins through the blood-brain-barrier to progressively destroy neurons. Animal studies had shown that the transmission of proteins through the barrier could be inhibited by infusions of large molecular dyes such a trypan red. Lacking any effective treatment, daily infusions of 1% trypan red in saline were administered. Lead Belly was a very black man and after a week of perfusions, his sclera, palms, and soles of his feet became brilliant red. He died in December 1949.

Face-Hand Test. Two teachers, Morris B. Bender[29] and Edwin A. Weinstein[30] encouraged interest in clinical research. While in the Naval medical service Bender, a clinician trained with the neurologists Israel Wechsler and Israel Strauss at Mt Sinai Hospital, became interested in the phenomenon of visual extinction on double simultaneous stimulation in a sailor with a parieto-occipital shrapnel wound. The interaction of simultaneous administered stimuli delineated sensory lesions better than single stimulation. Following professorial tradition he called me and my colleague Martin A. Green to his office, handing each a stack of 3x5 inch blank white cards, telling us to survey the responses of patients to simultaneous tactile stimulations of the face and hands – first in our patients on the Neurology wards, and then on the Psychiatry wards. When we had a hundred such records he asked that we find 100 normal children, then he sent us to Letchworth Village in Thiells, Rockland County to examine an equal number of the resident population of mental retardates.

Applying pin pricks or finger touches simultaneously to both cheeks or hands were correctly perceived by normal adults. But in patients with diverse brain dysfunction and diminished vigilance, as after head trauma, structural brain damage with bleeding, tumor, or stroke, one stimulus was reported and the other was not, even though the sensation of each single stimulus was readily perceived (extinction). At times the patients mislocated one of the stimuli on their body (displacement) and occasionally insisting that the stimulus was applied to space in

front of them (exosomesthesia). These phenomena were not explicable by classical neuroanatomy. The phenomena had been conspicuous in soldiers with severe head injuries and we reported the same phenomena in patients with abnormal brain syndromes, publishing reports on the Face-Hand Test (FHT) as a measure of whole brain dysfunction, the organic mental syndrome.[31]

Similar test abnormalities were demonstrated in normal children under the age of 6, and in patients with mental retardation with low mental age scores on Stanford Binet tests. The positive FHT was a rapid estimate of mental age, normalizing at age 6. Impaired brain functions in the elderly were demonstrated in those with impaired orientation and memory.

Injections of amobarbital increased omissions and displacements.[32] Sensory errors increased with injections of amobarbital during the course of electroshock therapy (when slow waves in the EEG became prominent after 3 to 9 seizures).

In later experiments carefully measured sensory stimuli demonstrated extinction as sensitive to the stimulus strength as well as the state of vigilance.[33] For a time the FHT was widely recommended as a "soft neurological sign" of brain abnormality but seems no longer to be so used.

Dalliance with Psychoanalysis

My interest in psychoanalysis developed during my neuropsychiatry training in Texas. It was 1946 and the enthusiasm for Freudian psychodynamic theory and practice infected psychiatric teaching and practice. The enthusiasm was strong with the belief that Freudian principles would explain the behaviors of the psychiatric ill and also offer effective treatment, personal understanding, and clinical relief. As a military veteran, I was entitled to educational training supported by the GI Bill. Like others of my peers, I decided to attend an analytic training program, applied to the psychoanalytic institutes in New York, and realized that the New York Psychoanalytic Institute and Columbia University programs required full-time attendance and clinic care of psychiatric patients. I would have to choose between my neurology training and full-time psychoanalysis. The William Alanson White Institute, however, organized its classes during evenings and week-ends, and I enrolled for their psychoanalytic course for physicians not for any faith in their beliefs but to continue my neurology training.

I began a personal analysis with a WAW graduate Dr. Joseph Miller, meeting for one hour three times a week for the next five years. The WAW did not see merit in the "Freudian couch" approach so the discussion was face-to-face. A psychological assessment by Dr. Ralph Crowley directed the early discussions. School classes were small with Clara Thompson, Ralph Crowley, Frieda Fromm-Reichman, and Janet and David Rioch among my teachers. David Rioch offered elective classes in neurophysiology and brain function that were held on Saturdays in Washington, D.C. We read the writings of Sigmund Freud, Karen Horney, Erich Fromm, and Harry Stack Sullivan, emphasizing the social aspects of interpersonal interactions rather than the classical studies of the unconscious and psychological defenses. I completed the school's requirements for a Certificate for Physicians in 1953.

During my year of residency at Hillside, my supervisor was Sidney Tarachow, a teaching psychoanalyst from the Columbia University School of Psychoanalysis. He enquired whether the presence of one or two parents during childhood influenced the expression of psychoneurosis. Did the absence of one parent by death, separation or divorce early in childhood encourage the expression of an obsessive-compulsive neurosis while the childhood presence of two parents was associated with a hysterical neurosis? It was a testable question. I examined the hospital records for those diagnosed with a psychoneurosis, abstracted the family history and evaluated the patient's main symptoms. We identified patients with dominating obsessive or hysterical symptoms and found 50 records with sufficient data for study. We did not find a difference in family histories to support the hypothesis.[34]

Another study of psychodynamic principles also failed to support a theory. I was assigned the care of a 26-year-old Jewish married man with panic episodes. The diagnosis varied between a neurosis with homosexual panic disorder or paranoid schizophrenia. Supporting the diagnosis of schizophrenia were his fantasies of aggression and the paranoid imagery on his Rorschach Test responses. I presented his story to an audience of psychoanalytic teachers. The discussion was robust in interpretations but inconclusive as to diagnosis and treatment options. The proceedings were published.[35] Re-reading this report after 60 years showed the many changes in our diagnostic styles, the rejection of homosexuality as a disease, the present tolerance of American society of homosexuality as a life-style, and the awareness that our later experience with medications would offer similar patients effective treatment with imipramine.[36]

Neither the teachings of Freudian scholars at Hillside Hospital nor the social psychological principles of the Sullivanian scholars at the William Alanson White Institute impressed me as useful therapies. Nor did I have the patience to indulge hour after hour, month after month, listening to a patient's anxieties, social difficulties, moods and fantasies. In time, my interests shifted and by 1958 I decided to close my private office and devote my life to a research career.

Electroencephalography (EEG)

Electrical rhythms from the intact human scalp were first described in 1929 by Hans Berger, a German psychiatrist. Within two years, in his third report, he described the changes associated with morphine, scopolamine, and other psychoactive drugs.[37] Spontaneous seizures and the rhythms of the inter-seizure EEG in epilepsy were next reported.[38] Would EEG recordings distinguish effective from ineffective treatments in the induced seizures of ECT? Could the EEG identify a successful course of treatment? Were the seizures induced by pentylenetetrazol the same as those induced by electricity or by insulin?

While I had seen electroencephalograms of patients as a medical student and a resident at Bellevue Hospital, I had no technical experience with the procedure. Reports of recordings during epileptic seizures induced by Metrazol, the chemical used by Meduna to induce seizures in schizophrenic patients, had dotted the literature since 1938 followed by similar descriptions for insulin coma and for ECT. During each procedure EEG frequencies slowed, amplitudes increased, and sharp, spike-like waves appeared. Missed and partial seizures induced little or no change in the EEG. Greater slowing of frequencies and increases in the duration and amplitudes of slow waves and spike activity marked more intense seizures. The altered rhythms persisted for weeks and, in a few patients, for months after the treatment course ended.

I sought training in recording and interpreting the EEG. As my residency at Hillside was to be completed in December 1952, I applied for a fellowship at the Mount Sinai Hospital in New York City beginning in January 1953. (By this time, too, after five and half years of postgraduate medical training I opened a private-practice community office in neurology and psychiatry, which I did in the summer of 1953 in Great Neck on Long Island.[39])

With Hans Strauss[40] and Mortimer Ostow[41] I learned how to apply scalp electrodes, maintain the EEG recorders, and interpret the records. The Medical Director Joseph S.A. Miller,

established an EEG Service with a Grass electroencephalograph purchased with a $5,000 grant from the Dazian Foundation obtained by Dr. Israel Strauss, the Founder of the Hospital. By the end of 1953 I had appointed and trained an EEG technician and developed a protocol for the study of the changes in EEG associated with ECT.[42] An application to NIMH funded a five-year study under Grant MH-927 "Altered Brain Function Following Electroshock" in the summer of 1954.[43]

Hans Berger had recorded rhythmic frequencies from 4 to 16 Hz. The more common 8-12 Hz waves were labeled *alpha* waves, the faster (>13 Hz) as *beta,* and the slower labeled as *theta* (4.0-7.5 Hz) and *delta* (<4.0 Hz) waves.

At first the changes were measured from baseline crossing to baseline crossing by a ruler to estimate mean frequencies. The peak amplitudes were measured for each wave using calipers. In our first study of the changes after induced seizures, the technician and I measured the number of waves in 10-second epochs for 60 to 120 seconds of artifact free samples for each weekly recording. We scored the records as *low, medium* and *high* degree changes. Since the recordings were done weekly, we had six to eight records for each subject. Progressive slowing of frequencies and increased amplitudes marked the treatment courses. In later records, bursts of slow waves with sharp spike activity were seen. The best clinical recoveries were reported in patients with high degrees of slowing and amplitude increases and we concluded that the EEG changes were necessary for the recovery of the patients.

EEG recording became the center of my research interest, studying changes during the hospital course of patients treated with ECT and ICT. We were unable to record the actual seizure as our instruments became "blocked" by the electrical stimulus. But we could examine the interseizure record. Treatments were given on Mondays, Wednesdays, and Fridays with EEG recordings done on a regular schedule for each patient on Tuesdays and Thursdays. These records showed progressive slowing with increasing numbers of treatments.

The grand mal seizure was necessary for beneficial effects. With increasing numbers of treatments the EEG rhythms slowed and the amplitudes increased. The patients whose inter-treatment rhythms changed very little did not recover from their illness. The development of these rhythms was necessary for recovery.

Necessary, but not sufficient, was soon shown by the failure of some patients to improve in whom these rhythms developed. At the time, we were treating a wide range of illnesses.

Many would meet criteria for major depression, bipolar disorder, and schizophrenia in the modern classifications. The schizophrenic patients, except those with the catatonic form of the illness, showed the least benefit to treatment. The specificity of seizure effects depended on psychopathology. Diagnosis became a critical process by which patients with high likelihood of benefit could be selected for treatment.

For the next four decades I studied and reported on the EEG effects of ECT and ICT; then the many new psychoactive drugs introduced after 1954; developed methods for quantitative measurement of EEG changes using digital computer methods; classified psychoactive drugs by their EEG characteristics; and developed and defended the concept of the "Association of EEG and Behavior with Psychoactive Drugs in Man."

Personal Affairs.

I married Martha Pearl Gross, a graduate of Barnard College on September 11, 1949. We met when I returned from a trip as the ship's surgeon on the Grace Line's *Santa Monica* in March 1948. Martha was dockside awaiting her parents who had been passengers on the cruise to Barranquilla and Cartagena. Her father was ill with amyotrophic lateral sclerosis, and as the ship's surgeon I was called upon for his care. When we returned, Martha met the ship. After I called on her parents at their home in Great Neck, we dated and married on September 11, 1949 after her graduation in June. I continued my training at Bellevue and in May 1951 our son Jonathan was born. We had an apartment at 404 East 54 Street in NYC. When I continued my training at Hillside, we moved to Martha's parents' home in Great Neck, about 10 minutes from Hillside. In early 1953 we bought a home in Russell Gardens at 11 Wensley Drive.

By mid-1952 I was coming to the end of my formal training and saw my future as a community practitioner in neurology and psychiatry. I opened an office in Great Neck, sharing one with Walter Glass, a specialist in Ear, Nose & Throat illnesses at 275 Middle Neck Road. An active practice of neurology consultations, psychotherapy, and modified ECT administered in the office. Amobarbital and succinylcholine were administered with the aid of a nurse.

Late in 1952, Hillside Hospital's Medical Director, Joseph S.A. Miller, asked me to supervise the ECT/ICT service on a half-time basis. I happily accepted as it offered an assured income while I built up a community clinical practice.[44] Two general medical hospitals opened with Long Island Jewish Hospital on the grounds of Hillside Hospital and another, the North

Shore Hospital in Manhasset a few miles nearby. I was appointed to the Neurology services of both hospitals, and organized their EEG Departments. My community practice bloomed, reports of the Hillside studies were being published and presented at national and international meetings, and our family grew with daughters Rachel born in 1956 and Linda in1958. I had to decide which of my activities to curtail. An offer of a full time appointment to Hillside at double my salary was so enticing that within six months I had closed my office, resigned from the hospital staffs, and since then I have been a full-time academic until my retirement in 2005.[45]

Move to Missouri - 1962

Although the Hillside research and clinical programs were progressing well, I sought connections to academia. Hillside Hospital was a free-standing institution without an academic connection. I had met George Ulett, Professor of Psychiatry at Washington University much earlier. He had studied the changes induced by the anticholinergic agents atropine and scopolamine on the EEG and behavior of ECT treated patients. He was a tinkerer with electronics and had built a Walter frequency analyzer from parts that had been excessed in the UK and then had built one for me in 1959.

In 1960 the State of Missouri was rocked by complaints that the state mental health hospitals were badly managed, with illicit drugs and pimping patients for sex so prominent as to threaten the Governor's tenure. He sought an independent Commissioner for Mental Health from the Washington University staff. Ulett was interested. Seeing a new 4-story building had been built on the grounds of the St. Louis State Hospital on Arsenal Street, about 20 minutes from the Medical School, Ulett decided to accept the appointment if the Governor agreed to establish and fund a State supported independent research center. Edward Gildea, the chairman of the Washington University Department of Psychiatry agreed to affiliate the Missouri Institute of Psychiatry with the Department. I was offered a Research Professorship in his Department and the promise of university appointments for scientists appointed to the Institute.

We found a home in the Lake Forest suburb, and our children were soon registered in their schools. Now that our youngest child was schooled daily, Martha enrolled at Washington University for an M.A. in Education and a lifelong teaching career.

We adjusted to a new community although warnings of religious intolerance appeared early. When we were looking for a home, I asked Ulett where he lived. "In Ladue," but

followed with the advice "You would not be happy there." I did not catch the warning but we soon experienced the strong smells of anti-semitism and nativism that pervaded the communities and state and hospital government during our stay. My appointment to the MIP was announced as "Austrian Heads Institute."

I soon experienced the complex maneuverings necessary to manage state government funds, the rigidities of the personnel of the agencies, and the Mussolini-like attitudes of the St. Louis State Hospital director Louis Kohler. He very much resented the separation of the Institute building on the grounds of his hospital to another fiefdom, insisting that his office be on the first floor of the new building.

I invited scientists to join the faculty, equipped the library and laboratories, and filled my time with a myriad of daily administrative decisions. Most frustrating was fracturing of the relationship with Washington University. At the end of 1962 Dr. Gildea retired and was replaced by Eli Robins, a laboratory scientist who had no interest in the community relationships that had been established with the psychoanalysts at Jewish Hospital, the overworked staff at the Malcolm Bliss city hospital, and our center at the St. Louis State Hospital. Robins dissociated himself from these centers and refused to consider our appointees to the teaching faculty. Nor would he send students or residents to our facility.[46]

Ulett arranged an academic affiliation with the Psychiatry Department at the University of Missouri in Jefferson City, a distance of 140 miles. Although our scientists were appointed to this Department the distance precluded an active teaching or research relationships with students or faculty.

We maintained an active program testing new drugs within the NIMH ECDEU program, developed a relationship with the Bakirköy Hospital in Istanbul, opened community clinics to support discharged patients using long acting neuroleptic drugs, wrote digital computer programs for EEG analysis using an IBM 1710 and then the IBM 1800 devices, and successfully argued the merits of pharmaco-EEG in man versus studies in animals, the Association hypothesis to identify psychoactive drugs in man.

The Missouri state government was funded on a biennium. When the MIP was established the Governor agreed that he would increase the next budget to $1,000,000. We had been very successful in obtaining NIMH support and when the next State budget was announced, the legislature incorporated the Federal funds within the budget without additional state funds.

Without stable state funding, the positions of the scientists was not assured and they quickly looked for other venues for their studies, taking their programs and NIMH grants with them.

Appointment to the New York Medical College - 1966

Although we had developed an interesting group of collaborating scientists with interests in psychopharmacology and EEG, Martha and I decided to return to New York. I had met Alfred Freedman, the chairman of the New York Medical College Department of Psychiatry, when we were together at Bellevue. He offered me a position as director of the Narcotic Addiction program at Metropolitan Hospital and facilities to continue my EEG studies at the Department offices at 5 East 102 Street. Although I had no experience with opiates and opiate dependence I was intrigued by the challenge. In June 1966 we returned to a home in Great Neck. I established an EEG laboratory with a digital analytic system based on the IBM 1800. Donald Shapiro, a computer scientist at Washington University who had programmed the digital analytic systems, joined me.

An EEG recording laboratory was established on the drug dependent ward at Metropolitan Hospital and a second, with the IBM 1800 analytic system, at the Department offices. Peter Irwin, a nephew of the Oregon psychopharmacologist Sam Irwin, joined as laboratory manager. A new team of clinician scientists was developed for the opiate-antagonist studies, another team for the Greek cannabis studies, and a third for the ECT studies at Gracie Square Hospital. The studies are described in the chapters on ECT, on opiates and cannabis, and the use of digital computer programs for EEG analysis.

Funding for the studies were mainly from grants to the New York Medical College and the International Association for Psychiatric Research. The foundation was established in 1967 to monitor funds awarded from government and private sources.

Stony Brook Medical School - 1972

ECT Studies Renewed. In 1973 I joined the faculty at the newly formed Stony Brook University Medical School on invitation of Stanley Yolles, the former Director of NIMH. We had met often to discuss cannabis and narcotic antagonist studies. I was pleased to accept his invitation to join the Stony Brook faculty with a tenured research appointment with space for my

EEG laboratory and the promise to open the ECT Service at University Hospital that was then being built. (The adult in-patient unit opened in the winter of 1980).

ECT was widely perceived (and is still today) as a treatment for patients with depressive illnesses, especially those with melancholia or psychotic depression. My patients at Hillside and at Gracie Square Hospitals were from the narrow population of hospitalized psychiatric patients. At GSH I witnessed experienced clinicians successfully treat depressed and psychotic patients with medical illnesses in which ECT use was commonly discouraged, even interdicted, by the lack of understanding of the biology of the induced seizure and fears that the electric stimulus would adversely affect the heart and the brain. I had seen ECT seizures to be remarkably safe and now that I was the responsible clinician in the choice of treatments I enthusiastically explored the challenges of patients admitted to a general hospital. We successfully treated depressed and psychotic adolescents and the mentally retarded, pregnant women, patients with brain tumors and aneurysms, with cardiac pacemakers, malignant catatonia, anemia, Parkinsonism, delirium, and pseudodementia.[47] I found ECT to be a benign and well tolerated procedure despite the image and language of "electric shock to the brain" and the pictures of the facial grimace and the shaking of the body that marked public images of ECT.[48] Inducing seizures is a benign and safe intervention when properly done in its modified form. It has fewer complications, lower rates of death and side-effects than treatments with psychoactive drugs. Our experiences at Stony Brook expanded guidelines for patient selection and optimized treatment procedures.[49]

Return to Hillside - 1997 to 2005

In 1994 I was asked by the NIMH to take part in the review of an application for support by the psychologist Harold Sackeim of Columbia University to compare continuation treatments of placebo, nortriptyline alone, and nortriptyline and lithium combination after successful ECT in depressed patients. The reviewers invited the researchers to add a fourth arm, of continuation ECT, but Dr. Sackeim demurred. The grant was at the point of failing support when the chairman Jonathan Cole suggested that a separate project be funded to compare continuation ECT and the lithium-nortriptyline combination. Collaborating with Charles Kellner at MUSC in Charleston, Teresa Rummans at the Mayo Clinic in Rochester MN, John Rush at the University of Texas in Dallas, and my unit at Stony Brook we applied for support for the parallel study. By

1996 the CORE study was funded with reductions in dollar amounts. The original application had been built on partial support from the Stony Brook Department. When the grant budget was reviewed, neither the SB chairman nor the Dean was willing to accommodate the additional staff support needed. I turned to John Kane at LIJ-Hillside and he agreed to accept the study at his center, appointing George Petrides as project coordinator to his faculty. I retired from the Stony Brook faculty and undertook the CORE study. I was appointed to the Albert Einstein College of Medicine faculty as Professor of Psychiatry.

By 1997 the project began at the four sites and for the next decade this program was the central point of my research and teaching activities. I had seen the need for proper training in ECT while at Stony Brook, and in 1997 established a 5-day "hands-on" teaching course with Sam Bailine and George Petrides at Hillside. As the CORE study progressed, we obtained additional support to compare the effects in unipolar and bipolar depressed patients and using bifrontal, unilateral and bitemporal electrode placements. By 2013 I summarized the findings of the19 reports of the 14-year study.[50]

Retirement

By 2005 I left the study group at Hillside and retired to my home in Nissequogue. Beginning in 1999 I spent my time writing articles and books with Michael Taylor, Jan-Otto Ottosson, Edward Shorter, and multiple colleagues on convulsive therapy, catatonia, ethics, and melancholia. My archives are now at the main library at Stony Brook. I continued to lecture and attend national and international meetings until this past year. As I write these lines, celebrated my 93rd birthday on January 16, 2016. I look forward to completing these reminiscences as experimentalist, researcher, editor and teacher.

03 Inducing Seizures: Hillside 1952-1962

To extend my experience in psychotherapy after three years of training in neurology and psychiatry I came to Hillside Hospital, a hospital noted for long-term psychotherapy of its patients. On my first day I was assigned to the electroshock and insulin coma treatment suites by the associate medical director Simon Kwalwasser.[1] Both treatments at the time were "unmodified," given without sedation or muscle relaxation. In ECT, patients lay on a wheeled stretcher under sheet restraints, a rubber bite-bloc placed between their teeth, two stimulating electrodes appliedat the temples, and a seizure induced with currents delivered from a Medcraft alternating or a Reiter polyrhythm current device with the energy set according to estimates of what was needed to induce a full grand mal seizure. As the currents were applied, the neck and back arched, the body became rigid, followed by rhythmic muscle movements and breath holding. The patient became cyanotic with blue lips. Movements stopped, the muscles relaxed, deep breathing followed, cyanosis waned, and color returned to the lips as the patient was moved to a recovery room. The patient was cared for by aides until able to get off the stretcher on their own and walk to the ward for shower, dressing and breakfast. Durations of the elicited seizures varied in length from 30 seconds to a few minutes, occasionally requiring termination by intravenous amobarbital.

Observing a full grand mal seizure in each patient jarred me. The previous week and for years before I had been taught by my neurologist teachers that seizures were dangerous to patients and must be stamped out. Every teacher had emphasized the need to fully inhibit seizures to avoid tooth, limb, and spine fractures, tongue-biting, confusion, injury from falls, and death. And now, I was deliberately inducing grand mal seizures! This antithesis has plagued my professional life and the lives of neurologists who, to this day, are unable to accept the evidence that benefits accrue to severely depressed, manic, catatonic, and psychotic patients with repeated induced seizures. As I learned how to treat patients safely I realized the remarkable benefits of inducing seizures, and such treatments became a central interest for the remainder of my professional life.

After the introduction to ECT that first morning, Kwalwasser led me across the hall to the insulin coma treatment unit, a well-lit air-conditioned suite of 22 beds with a large nursing staff. Cries, coughs, grunts, and occasional screams of patients filled the room, with some patients in coma, some drowsy and confused, and some suffering a seizure.

They had come to the treatment unit in loose-fitting pajamas at 6 in the morning and had been injected subcutaneously with measured doses of insulin. For the next three to five hours they were repeatedly examined as they lost consciousness, their tendon and pupillary reflexes disappeared, breathing became stertorous, and intense sweating soaked the sheets.

After a measured hour, stupors were ended by 10% glucose solution administered either by nasogastric tube or by intravenous injection. The change from unconsciousness to consciousness and to talking with the aides occurred rapidly, within 10 to 30 minutes. On awakening, each patient was taken to shower, dress, and within an hour was eating breakfast. Most were famished and ate everything put before them.

Insulin coma treatments, like the ECT sessions at the time, were unsafe. Fractures of teeth and limbs occurred and confusion persisted for hours after treatment. Spontaneous grand mal seizures occurred during 20% of the ICT treatments, so that there was at least one unscheduled emergency every morning. For the patients who had shown little change in behavior during the course of treatments, seizures were also induced electrically in the midst of the coma. This combination of ECT and coma was common for the severely psychotic patients, an implicit recognition that the seizure was the therapeutic feature of the coma treatments.[2]

Occasionally, consciousness did not return despite repeated doses of glucose. Stupor persisted with sweating, fever, elevated blood pressure, and rapid heart rates. We had no understanding of why the state occurred nor how to relieve it. Many experimental means were tried. Relief from the stupor occurred slowly over days of intensive nursing care. Two patients died in the six years that I was on that service.

By early afternoon, the ICT and ECT treated patients were with their physicians in individual and group treatment sessions, meeting relatives, participating in occupational activities, and playing games. I tested their skills in chess and checkers, frequently finding their skill better than my own despite their morning seizure or coma. It was remarkable to see a young patient in coma, unresponsive to verbal, sensory, or painful stimulation and an hour later chatting with staff, drawing, and playing games or musical instruments. Older patients, though, were more often confused and fatigued, spending a good part of their post-treatment day in their rooms or in their beds.

For the next three months, I managed both treatments, with ECT three times weekly and ICT every morning. My afternoons were spent in individual sessions with patients, meeting families, attending conferences about individual patients and classes with attending physicians.

Of the hospital populations, the patients treated with electroshock improved the most. They became more cooperative and responsive, no longer expressing morbid thoughts and threats of self-harm, sleeping and eating better, and interacting more normally with their families and other patients. The outcomes with insulin coma were less well defined, and the risks much greater, but yet, greater percentages of patients so treated were rated improved than after psychotherapy.

ECT treated patients typically improved rapidly; many returned home, with few transferred to the local State Hospital for lack of improvement. By contrast, few insulin coma treated patients returned home after a year's residence; most continued in chronic care. A 5-year follow-up study of 314 patients admitted to the hospital in the year 1950 reported a mean hospital duration for ECT-treated patients of 5.0 months, for psychotherapy-treated patients 6 months, and for ICT-treat patients 6.5 months.[3] With ECT, 76% were rated as recovered or much improved compared to 53% for psychotherapy and 33% with ICT. Admittedly, the selection of treatments and the diagnostic labels were not random but dictated by the opinions and beliefs of the Attending physicians and by the preference for courses of psychotherapy before assignment for ECT or ICT.

The teachers had social and symptom guidelines for diagnosis and treatment. The younger, more literate, and better educated patients with phobias, obsessions, compulsive rituals, and anxiety states were assigned a diagnosis of psychoneurosis and valued as candidates for psychotherapy; the more aggressive, over-active, and psychotic patients were labeled schizophrenic, with ICT or ECT the recommended treatments; while the elderly, poorly educated patients, often immigrants, were seen as depressed and referred for ECT.

By mid-year I had learned that ECT effectively reduced suicide thoughts, negativism, aggression, and depressed and manic moods. I read articles on how the treatments originated, the central role of the seizure, and the various ways it had been induced -- by chemical means or by electricity. Little was known about the systemic effects, but recording the brain seizure by electroencephalography (EEG) were being reported. Hillside Hospital did not have an EEG service but it did have a Medical Department whose physicians were interested in the changes in

the body during and after these treatments. EEG recording offered understanding of the physiologic effects in both treatments.

If spontaneous seizures are signs of the brain's illness in the epilepsies, how can a fit relieve suicidal thoughts, manic excitement, and catatonic stupor? Theories abounded, but none was grounded in experiment. Hypotheses were highly imaginative, ranging from the psychological denial of illness proffered by my teachers; reassessment of living after intense fear and repeated sensations of death that brought life into a more positive light; erasure of painful threatening memories; chemical changes in endocrine functions; a renewed wish for life after punishment for bad behaviors; and on and on. [4] Most of these accounts were subjective and not quantifiable. We needed a better, physiologic measure of change in response to treatment. I turned to the electroencephalogram (EEG) hoping to develop one.

Interest in Electroencephalography

In 1771 the Bolognese physician Luigi Galvani had demonstrated that an electric stimulus caused a living frog muscle to twitch and contract. He observed electric currents from living muscles by the movements of a magnetized "galvanometer" needle. His experiments connected the newly discovered phenomena of electricity to living tissues.

A century later, in 1875, the physiologist Richard Caton recorded electric oscillations from the exposed brain of a living animal, securing the connection between brain functions and electricity. But these currents were too small to be recorded through the skull and could only be demonstrated in an exposed brain. Then, in 1929 Hans Berger, a Jewish hospital psychiatrist in Jena, Germany, recorded electric oscillations from electrodes on the intact human scalp adapting the device used to record the electrical activity of the heart. The rhythms varied with changes in vigilance, sleep, body physiology, and the effects of systemic drugs. In his third report two years later Berger described changes in the EEG under the influence of cocaine, scopolamine, morphine, chloroform, and sleep. The electrical changes associated with insulin-induced hypoglycemia (as in insulin coma therapy) and the chemical and electrical induction of seizures were next charted, as these treatments were increasingly applied in the severe mentally ill.[5]

For the next four decades I studied and reported the EEG effects of ECT and ICT, and of the many new psychoactive drugs introduced after 1954.[6] I adapted methods for quantitative measurement of EEG changes first using an electronic frequency analyzer and then digital

computer programs. I classified psychoactive drugs by their EEG characteristics; and developed and defended the concept of the *association of EEG and behavior with psychoactive drugs in man*, a concept that was in conflict with the widely established belief in academia and in industry that the EEG and behaviors after medications were unrelated, as had been reported by pharmacologists studying the effects of the new drugs in animal species.[7]

Establishing Hillside's Department of Experimental Psychiatry

Once the EEG laboratory at Hillside was established and the NIMH had awarded funds to study the EEG changes in ECT, I sought colleagues and the hospital obligingly established a Department of Experimental Psychiatry. Our first study examined the relation of the slowing of EEG frequencies during the ECT course and clinical improvement. The study team tested various forms of electricity to stimulate the seizure, compared the efficacy and behavior effects of different electrode placements, compared seizure to non-seizure treatments, and measured the changes in psychological tests associated with treatment. In 1961 I summarized our experiences in a report[8] that became the core material of the studies described in my 1979 book *Convulsive Therapy: Theory and Practice.*

The laboratory of experimental psychiatry grew rapidly, especially as new psychiatric medicines began coming on the scene. Two full time clinical psychiatrists, John C. Kramer[9] and Donald F. Klein[10], took part in dose-finding medication studies, and the behavior changes measured using the Lorr Behavior Rating Scale. My neurology training colleague Martin Green[11] led the EEG studies and Joseph Jaffe[12] studied the changes in recorded speech patterns. The psychologists Robert L. Kahn,[13] Max Pollack,[14] Nathaniel Siegel,[15] Hyman Korin,[16] and Ira Belmont joined the department to tease out changes in patient responses to the Rorschach, California F Scale, and Hollingshead and Redlich Social Class psychological tests, and responses to tachistoscopic exposure to complex images.

The Denial Hypothesis.

I had come to Hillside after studying neurologically ill patients and had learned to recognize the phenomenon and language of "denial of illness," when misery was pictured as less threatening or denied as ever having existed. Edwin Weinstein and Robert L. Kahn codified such experiences in the monograph "*Denial of Illness*" in 1955. I had worked with both

colleagues at Bellevue and they, as we have seen, had identified denial language and its increase with amobarbital as characteristic of abnormal brain functions.[17] As denial language is enhanced by injections of amobarbital, the EEG rhythms also slow and amplitudes increase. The changes in language and in EEG rhythms were described as the development of *organic brain dysfunction*.[18]

With ECT, depressed patients become euphoric in mood, deny their symptoms of illness, and became less oriented in time and location. These changes are welcomed as "recovery." (In our studies of patients treated with new psychotropic drugs we also saw increased denial and euphoria, a phenomenon that we labeled the *euphoric-denial* adaptation.[19])

During ECT,patients develop difficulties in properly identifying multiple sensory stimulations making repeated errors in the Face-Hand Test. Sensory stimuli are mislocated when two are applied simultaneously, usually reporting only one stimulus (extinction), occasionally mislocating a stimulus across the side of the body (anosognosia) or into interpersonal space (exosomesthesia). They smilingly deny illness and no longer recall the moods or thoughts of their illness, even when reminded. These findings of the changes accompanying ECT brought to mind my similar experience with head injury patients. At the time, I accepted denial of illness as my favored explanation for the recovery with ECT.[20] It was logical, supported by experimental tests, and encouraged by my teachers. There was much that still remained unclear, however.

Once our Hillside EEG laboratory was established and we were recording EEG patterns during the ECT course for each patient, we made similar recordings for those treated with chlorpromazine, the first of the new drugs that altered human behavior without undue somnolence, that marked the new psychopharmacologic era in psychiatry. By 1954, the first clinical tests of chlorpromazine had found it to be effective in reducing aggression, excitement, and paranoid thoughts in patients. With increasing dosages of the drug, the EEG frequencies slowed, but with smaller changes in amplitudes than the rhythmic bursts seen in induced seizures.

Once I became comfortable in eliciting seizures in patients, research questions tumbled one after another. My experiences with researchers during medical school, internship, and residencies helped me develop a questioning attitude and recognize the importance of recording

data.[21] It was also a golden time in human clinical research with studies accepted by patients and society.[22]

Optimizing ECT Procedures

At Hillside electroshock treatments were initially given "unmodified" -- without sedation or muscle paralysis, allowing the full grand mal seizure to develop in each treatment. For anxious patients, amobarbital was injected to sedate and relax. We also interrupted the longer seizures by injections of amobarbital.

The body movements, EEG seizure patterns, and changes in physiology are similar for each treatment. Indeed, the "seizure" has the same form and is readily recognizable in all mammals. It is an inherent pattern that occurs both spontaneously and when stimulated by electricity, by chemicals, and by disease. What is the function of such a universal response? In natural environments a seizure puts the subject at undue risk of predators and one would expect that after generations the behavior would be extinguished by natural selection. But the biology persists. Does the seizure serve a useful purpose, then, and if so, what is it? Such ruminations puzzled me then, and puzzle me still.[23]

Fractures of teeth, vertebrae, and long bones were unfortunately common occurrences. Many forms of physical restraint and chemical inhibition were tested. Curare, for example, a biological preparation made from South American plants, prevented both the tonic (increase in muscular tone, stiffening of the body muscles) and the clonic movements (rhythmic movements of the stiffened musces) of the seizure. But curare was heat sensitive and the samples were unstable. In some patients it effectively blocked the motor movements and in others, though, the effects were small and a full seizure occurred. A dose on one occasion might effectively modify the seizure, but in the next, the same dose would fail to relax the patient. On occasion, paralysis persisted after the seizure and it was necessary to administer oxygen through a mask until natural breathing returned. We discontinued curare use and depended on sheet restraints alone to prevent fractures.

Spine x-rays were taken in 50 patients before unmodified seizures and repeated in the week after the last treatment. In seventeen patients a compression fracture of lumbar vertebrae 4 or 5 or both was recorded. Surprisingly, these fractures elicited little complaint from the affected patients. Such compression fractures were accepted as a price of the treatments.

In the spring of 1953 a new synthetic muscle relaxant suxamethonium chloride (succinylcholine) was introduced. The onset of limb paralysis within 30 to 60 seconds of intravenous injection, and dissipating within a few minutes of its application made it an ideal agent for ECT. In our first experiences we had not pre-sedated the patient, succinylcholine was injected, and when muscular twitchings (fasciculations) and a weakened knee jerk were seen, the seizure was induced. Tonic arching and clonic movements were much weakened. Spontaneous breathing returned quickly and the patient was moved to the recovery room. We injected our second patient, induced a seizure, and then we heard cries of "I cannot breathe, I cannot breathe" coming from the recovery room. Oxygen was administered by mask only to have the same experience with the next patient.

Thereafter, we induced amnesia in every patient with amobarbital or thiopental before the succinylcholine injection. As more physicians studied this method of muscle relaxation, "modified ECT" was broadly accepted -- sedation by a barbiturate, oxygenation by mask, injection of succinylcholine, and seizure induced when motor fasciculations and diminished ankle or knee jerk were recognized. Although my initial experience was in a hospital setting, most treatments were administered in office settings, such as in my office in Great Neck, where I treated patients in the early evening hours assisted only by a nurse.

The practice of "modified ECT" was confusing, though. What was the role of the preliminary sedative -- to induce sleep, reduce anxiety, or block memory of the procedure? After the 1960s and 1970s, as ECT was reintroduced and "anesthesia" became the province of anesthesiologists, psychiatrists administering a sedative and the muscle relaxant was no longer tolerated, effectively ending ECT in independent office settings.

New sedation agents were studied. Benzodiazepines were tried, only to find that the induced rise in seizure threshold interfered with treatment outcomes and reduced treatment efficacy. Methohexital offered the proper efficacy, safety, and short duration of action, replacing amobarbital. New anesthetic agents – propofol, etomidate, ketamine, isoflurane –were tested. Propofol raised seizure thresholds, and the enthusiasm among some practitioners for minimal energies to induce seizures led to ineffective treatments and poor outcomes. Etomidate became fashionable for a time but the sedation was slow and injection sites often became inflamed. We found an application for ketamine in excited delirious patients. An intramuscular injection in a

patient restrained in bed would quickly sedate so that the patient could be moved to the treatment room and succinylcholine safely administered.

By the 1980s "modified ECT" had become the universal standard, but not universal practice. In some countries the expense of the additional chemicals and the belief in the need for an anesthesiologist led either to the inhibition of treatments or continued use of "unmodified" treatments.[24]

The EEG of Electroshock

The EEG brain rhythms in alert normal adults are filled with 8-to-12 Hz (*alpha*) frequencies and with amplitudes of 40 to 80 microvolts (μv). Patterns vary with age, during day and night, and are altered by drugs and disease. After head injury and intracranial bleedings, the rhythms slow with increasing amounts of *theta* (4.5 -7 Hz) and *delta* (2-4 Hz) frequencies and the amplitudes increase from 50 μv often to 150 and 200 μv. As brain pathology improves, normal EEG rhythms return.

During my EEG education I was shown records with high voltage slow waves with "spikes" appearing in one-to-three second bursts with longer runs of lower voltage slow waves as evidence of an epileptic seizure. We found similar records on inter-treatment days during the course of ECT. The pre-treatment records of our psychiatric ill did not differ from those of healthy individuals, with older patients showing slower rhythms than did the younger.[25] In the minutes and first hours immediately after a seizure, EEG voltages increase, frequencies slow, and burst patterns appear In ensuing days, the changes after each treatment persist for longer and longer periods. After 4 to 10 treatments, slow waves persist throughout the day, then for many days and in some patients for weeks thereafter.

It was technically unfeasible to record the actual seizure as our instruments became "blocked" by the electrical stimulus.[26] But we could examine the "interseizure" record, the changes in the resting EEG record on days between treatments. Seizure treatments were administered on Mondays, Wednesdays, and Fridays with EEG recordings done on a regular schedule for each patient on Tuesdays or Thursdays.

Brain electrical rhythms progressively slow and amplitudes increase during the ECT course, just as they do after head injury or intracranial bleeds. After the treatment course ends, the pre-treatment rhythms slowly return, not to the pre-treatment patterns but to more rhythmic,

regularized alpha frequencies. The changes induced by seizures induced by electricity and by the chemicals Metrazol or flurothyl are not distinguishable, arguing that the EEG records during treatment are related to the seizure and not to the seizure-inducing agent.[27]

Progressive slowing of interseizure frequencies was necessary for beneficial behavior effects. The patients whose inter-treatment rhythms changed very little did not recover from their illness. At the time, we were treating a wide range of illnesses. It was the era dominated by psychoanalytic concepts that minimized clinical diagnosis. Our patients would meet today's criteria for major depression, bipolar disorder, and schizophrenia. The more severely melancholic, particularly the elderly, responded well while the schizophrenic patients, except those with the catatonic form of the illness, showed the least benefit. Individual psychopathology became important in our understanding of the seizure therapies and was the motivation for my later studies of melancholia and catatonia.[28]

Although it was customary to describe the rhythms in non-quantitative descriptive terms, I sought more reliable indices, measuring the frequencies and amplitudes by height and width of each wave, using calipers and ruler, one wave after another, in 10-second epochs, up to 60 seconds for each sample, with an average of 600 waves measured at baseline and 350 to 450 waves at the end of a course of treatment.[29] By comparing numbers of treatments and degree of slowing for each patient, we found that slowing occurred earlier and to a greater degree in patients exhibiting symptom relief than in the patients whose behavior changed slowly or failed to improve. EEG frequency slowing and amplitude increases became markers for us of the brain changes that underlie behavioral improvement.[30] The rate and amount of change varied with electrical dosing and the number and frequency of treatments.[31] We concluded that EEG change was necessary for the clinical changes to take place and were markers of the physiological changes that are the basis for the treatment response. This lesson became the critical observation of the ECT process and became the core of my studies to optimize and understand the convulsive therapy process.

That the changes in EEG rhythms were similar to those in epilepsy and after head trauma was often used to justify an anti-ECT prejudice voiced by the public, by former patients, and by psychiatrists and psychologists who argued that seizures "damage the brain." But the EEG changes induced by the seizures were necessary markers for the clinical benefits; without such persistent slowing, recovery of illness did not occur.

The patient referred for ECT at the time, and even today more than a half century later, is very ill, unable to function at home or at work, is sad and unhappy, expressing thoughts of suicide, strange ideation, and often with aggressive manic behaviors. Almost all have been treated by many different regimens of pills, psychotherapy, vacations, diets, and anything else that the family or clinician can conceive as possibly effective before the patient is exposed to electroshock, widely conceived as hazardous and life threatening.[32] The patients met today's diagnostic criteria of major depression, bipolar disorder, and schizophrenia. The quickest resolutions of illness occurred in the severely depressed, suicidal, catatonic, manic, and delirious patients. The least benefits, despite changes in their EEG recordings and extensive numbers of treatments were in the withdrawn, apathetic, poorly motivated, thought-disordered patients who today meet the criteria in the standard diagnostic system for schizophrenia or bipolar disorder.

Anticholinergic Drugs and EEG and Behavior

In the 1950s little was known of the physiology of the slow rhythms in EEG after induced seizures other than that their presence was necessary for a clinical benefit. As the significance of EEG slow-wave activity was recognized, the chemistry of seizures was studied. George Ulett and LaVerne Johnson in St. Louis showed that the anticholinergic atropine and atropine-like drugs blocked both post-seizure EEG slowing and the anticipated behavioral recovery after ECT.[33] Herman Denber reported that injections of the chemical diethazine, another agent that reduced cholinergic activity in the brain, reduced EEG slow wave activity after ECT.[34] We replicated his finding for diethazine and also found that the antiparkinson agent procyclidine and various experimental anticholinergic drugs known as the JB-series reduced post-ECT slow wave activity. When anti-cholinergic drugs were introduced late in the course of ECT, when mood and thought disorders were relieved, the reversal was accompanied by behavioral worsening – patients no longer expressed denial language and increasingly complained of the recurrence of their symptoms. A day later, when EEG slow-wave activity had again returned, symptom relief was again expressed.[35] We associated EEG slowing is a consequence of increased brain cholinergic activity. Puzzling over the brain effects of repeated seizures led me to consider a cholinergic hypothesis for the recovery with ECT, as I describe in Chapter 8.[36]

Neuropsychological Tests and EEG Slowing

Immediately after a seizure, the patient awakens in confusion, poorly oriented as to location, date, or month, and unable to recall the names of the attendant personnel. Commonly, the recovery is complete within an hour. The duration and severity of a patient's errors in response to questions vary with the number and frequency of seizures, the sedative and electricity doses, most important the patient age with elderly patients confused for longer periods. With recovery, orientation normalizes and patients return to home, school and work. We tested the responses on the Face-Hand Test and found normal responses in the weeks after the last treatment, though the elderly persisted in making errors so long as EEG slowing of frequencies were present.[37]

With increasing numbers of treatments, denial test scores and the changes with amobarbital paralleled scores on EEG measures, as earlier research had suggested. Persistence in denial were more often scored in older patients, in the less well-educated, and in immigrants.[38]

The responses of ECT patients to other neuropsychological tests were also explored. Scores on the Rorschach test were loosely correlated with the treatment outcomes but the specificity, the predictability of the Rorschach criteria was low.[39] Social attitude was tested by the 10-item California F-Scale, a measure of prejudice and authoritarianism that became of considerable interest in the wake of the Nazi-Fascist eras.[40] The patients with high authoritarianism scores were more likely to show benefits from ECT.

Are Subconvulsive Treatments Effective?

Were the benefits of electroshock and insulin coma inherent in the changes in physiology associated with seizures or in the patient's panic and fear? What was the role of electricity and the seizure? To address these questions, we induced sleep using amobarbital, muscle weakness by succinylcholine, and controlled the dosage of electricity at levels that did not induce a grand mal seizure. These methods reliably elicited "subconvulsive" non-seizure "treatments."

Patients referred for ECT were randomly treated either with currents that induced seizures or currents that did not. Of 24 patients in whom seizures were induced, 17 responded clinically and were discharged from the hospital; of 27 patients treated with subconvulsive sham currents, only 4 responded. Nineteen of the non-responders went on to convulsive treatments and 16 became responders. The EEG recordings of the subconvulsive treatments failed to show

characteristic slowing. We confirmed that subconvulsive treatments were clinically ineffective and supported our belief that the therapeutic benefit was inherent in the seizure and not in the passage of electricity alone. These findings ran parallel to those of a well-designed study conducted by George Ulett in St. Louis that also confirmed the seizure as essential to the treatment's benefit.[41]

I published the results of our study in my 1979 textbook *Convulsive Therapy*. That year the British psychologist Timothy Crow challenged the profession to prove the necessity of the seizure to relieve depressive disorders.[42] His challenge was so convincing that multiple British-government supported studies were undertaken with results presented in an all-UK conference in September 1979 in Leicester, and in a published appraisal edited by Robert L. Palmer.[43] None of the studies with non-convulsive treatments supported clinical relief, reconfirming the critical importance of the induced seizure.[44]

A*re Chemical-induced Seizures as Effective as Electrical?*

In 1959 flurothyl (Indoklon), a new seizure-inducing chemical agent was proposed as a replacement for the electrical induction. Hexaflurodiethyl ether, a volatile congener of the inhalant anesthetic diethylether, is both anesthetic and seizure-inducing. After a few inhalations the subject loses consciousness; additional breathes elicit a full grand mal seizure, usually within a few minutes.

Four research teams – Joyce and Iver Small at University of Indiana,[45] Albert Kurland at the Maryland Psychiatric Center,[46] Björn Laurell in Sweden,[47] and I and my associates at Hillside Hospital[48] compared the effects of flurothyl and electrically induced seizures. Seizures were readily induced, with similar motor, seizure and interseizure EEG patterns. Both were clinically effective. Flurothyl seizures were of longer duration. Laurell reported lesser retrograde amnesia with flurothyl. In our randomized assignment study of patients referred for ECT, 15 patients received unmodified flurothyl seizures and 12 unmodified ECT. The clinical benefits, behavior patterns, fracture rates and degrees of EEG slowing were the same.

For lack of an identifiable advantage over electricity, the induction of seizures by flurothyl fell by the wayside. The drug's high cost and persisting ethereal aroma were deterrents. The smell was unpleasant, objected to by both our patients and our staff. Further, the ease with which a seizure was induced frightened the professional staff as the treatment room soon was

suffused with an ethereal aroma. Installing an in-wall exhaust air conditioner reduced the smell and mitigated the fears, but could not eliminate them. No advantage for flurothyl seizures was seen and we abandoned the method.[49]

Decades later, the pre-occupation with memory loss, encouraged by the psychologist Harold Sackeim and his colleagues, led to widespread reduction in treatment efficacy because many practitioners shifted to unilateral electrode placement and minimal ultra-brief currents. Increasing reports of treatment failures sent me to re-assess the experience with flurothyl as a potential non-electricity seizure induction method.[50] In the first quarter of the 21st Century, when repeated hospital site procedures for renal dialysis and chemotherapies and radiation for cancer are widely accepted, the re-establishment of anesthesia sessions using flurothyl could well achieve the therapeutic advantages of induced seizures without the fright associated with electricity and the words "electric shock." The review showed that flurothyl-induced seizures were clinically effective, that the effects on cognition and memory were less, encouraging a reassessment of flurothyl seizures. Alas, I failed to entice any clinician to undertake such a reassessment.[51]

From ECT to Psychopharmacology.

Despite a wide variety of examinations, tests, and hypotheses proposed and many useful findings, we had failed in the decade of the 1950s to develop reliable predictors of either good outcome from ECT or how best to select patients for clinical trials. For the most part, the referred patients were the mainstays of sanitaria treatments: those with persisting mood and thought disorders and had not responded to psychotherapy, sedation, and nursing care. Each clinician developed personal images of the behaviors that led him to refer patients for ECT. By 1960 the importance of the seizure was well established, with EEG changes recognized as necessary though not sufficient for positive outcomes. The value of treatment in melancholic and psychotic depressed patients was well established, as was the relief in delirious mania and catatonia. As the enthusiasm for the newly marketed psychoactive drugs increasingly dominated psychiatric practice, interest in ECT faded. The demonstration that chlorpromazine was as effective as insulin coma ended the latter's use, and the limited benefits of lobotomy and the high morbidity rates in seizures and strokes ended lobotomy's use. By the 1970s, critiques of

authoritarianism in state mental hospitals burgeoned, State anti-ECT regulations increased, and usage declined.

The successful experience with chlorpromazine and imipramine followed by the introduction of many newer psychoactive drugs soon shifted my research interest to the application and physiology of medications.

04: Interest in Seizures Renewed After Missouri Hiatus

During my four-year sojourn at the Missouri Institute of Psychiatry an ECT facility was not open to me -- psychopharmacology and quantitative EEG were the focus of my research interests. Soon after I returned to New York in 1966 to direct studies of opioid abuse at Metropolitan Hospital, I received a letter from Richard Abrams, an Army medical officer scheduled to join the college medical residency program the following July, asking if I would meet him at a December conference of the Association for Research in Nervous & Mental Diseases (ARNMD) in New York City.[1] He had compared the clinical efficacy and effects on memory of ECT using non-dominant unilateral or bilateral electrode placements at a military hospital. He had administered seizures three times or five times weekly for 20 treatments in 10 subjects and reported no difference in efficacy nor in cognitive effects between treatments of the two electrode placements. He wanted to continue such studies and asked for my support and collaboration.[2] I was still interested in understanding the mechanism of electroshock and agreed to support his studies.

New York Medical College's Department of Psychiatry lacked an ECT treatment unit at any of its clinical sites. The department chairman, Alfred Freedman, referred me to Lothar Kalinowsky, a member of the teaching faculty, who was treating his ECT patients at Gracie Square Hospital (GSH), a private hospital facility on East 76th Street in Manhattan. Kalinowsky was an early student of ECT, having witnessed its first applications in Rome in 1938 when he was studying with Ugo Cerletti and Luigi Bini, the originators of electroconvulsive therapy. He had published a leading textbook on the somatic therapies in 1946.[3] He agreed to be a consultant to our work, arranged for GSH Medical Board approval of the study and for the collaboration by the clinicians who treated their patients in the hospital.

Abrams and I asked: First, what is the optimal placement of electrodes in inducing seizures? We randomized patients to seizures induced with either non-dominant unilateral or bitemporal electrode placements, measuring clinical, cognitive, and EEG changes at weekly intervals. And, second, could the treatment course be shortened by applying multiple treatments in one sitting? Recognizing that most patients recovered from a melancholic depression after 6 to 10 seizures, Paul Blachly, an Oregon physician, had reported that multiple seizures in one session were as effective as the same number of seizures spaced over many days.[4]

We received four-year funding from NIMH for the project.[5] After we introduced the study to the GSH practitioners, many agreed to cooperate and to let us treat their patients according to our protocols. They endorsed their patients' cooperation for EEG and psychological tests. Aside from Richard Abrams and myself, our study collaborators were Jan Volavka, Jiri Roubicek, Rhea Dornbush, and Stanley Feldstein from the Biological Psychiatry Research division of the New York Medical College.

The Difference Electrode Placement Makes.

We tested 76 patients with a mean age of 63.4 years, 43 treated with bilateral and 33 with unilateral placements.[6] By diagnosis, 60 patients were endogenous depressed and 16 reactive (neurotic) depressed, two forms of depressed illness that are treated with ECT.[7] At the time, unilateral placement was considered less efficient in generating seizures and indeed some patients in the sample required additional seizures during their treatment course.[8]

We found bilateral ECT to be clinically more effective than unilateral ECT, with better and earlier outcomes regardless of age, number of treatments, or coincident medications. The effects on memory tests during the treatment course were less in the unilateral treated patients than the bilateral, varying with the task selected.[9] On auditory tasks, the patients receiving bilateral treatments showed greater decrements than those receiving unilateral treatments; on a visual task, however, performance was unimpaired by either treatment.

The slowing of EEG frequencies was greater after bilateral placement than after unilateral. An asymmetry was also observed: EEG slowing was accentuated on the right side with right unilateral electrode placement. In bitemporal treated patients the accentuation was on the left side. [10,11] Although we did not understand the significance of either the degree of slowing nor the sidedness, these findings confirmed that the degree of EEG slowing was related to clinical outcome. The lesser EEG changes and asymmetry of unilateral ECT were signs of lesser physiologic changes--and lesser benefit compared to bilateral ECT.[12]

Can Multiple ECT Treatments Per Session Shorten the Treatment Course?

In 38 patients we applied either 4 or 6 seizures within a single anesthesia session. Different placements – bitemporal, non-dominant unilateral, or anterior frontal -- were tested. Only one patient achieved clinical remission after one session through bilateral electrodes,

though we thought the benefits were accelerated in several others. The degree of EEG slowing was not enhanced, however, and the asymmetries were the same as we found in our singular treatments.[13] Post-ictal sleep among the MMECT patients was prolonged with greater disorientation and clouding of consciousness especially among the older patients.[14] Neither we nor the experienced clinicians whose patients we treated were convinced that multiple treatments in a single session were an effective modification.[15]

Weconfirmed Richard Abrams' experience that unilateral electrode placement could elicit effective relief with lesser effects on cognition, but at a price of lesser efficacy. Seizures induced through unilateral electrode placement, even with the maximal energies of alternating higher energy currents, were less effective than those developed through bilateral placements. The physicians at GSH, leading practitioners with extensive clinical practices, were not surprised by our results. Many, including Renato Almansi, David Impastato, Lothar Kalinowsky, and William Karliner, were emigres from Europe who previously had each tested different electrode placements, electric currents, and dosing schedules and had concluded, based on their clinical experience, that unilateral placements were inefficient, requiring more seizures for relief and entailing higher early relapse rates.

EEG Variations and Behavior

At Hillside Hospital I had seen a connection between the expression of increased EEG slow wave activity and clinical outcomes, concluding that EEG changes were necessary physiologic changes for the clinical benefit. The patients treated at Hillside were hospitalized psychiatric ill, with diagnoses of schizophrenia, manic depressive illness, and psychoneurosis being the most common. The outcomes varied from quick resolution and recovery among the depressed to little improvement among the schizophrenic and psychoneurotic patients.

The patients treated as out-patients at GSH were depressed older patients, resident at their homes, not needing hospital care. Their recovery rates were very high. The physicians had developed skills in patient selection assuring high rates of clinical relief, and all the patients developed greatly increased EEG slowing with treatment. I had expected that we would verify the relationship between the degree of EEG slowing and clinical response in the GSH samples. But we did not. The practitioners were so successful at selecting patients who would respond to treatment that we lacked a comparison group of patients with poor treatment outcomes![16]

Studies at Stony Brook

In 1973 I was invited to join the faculty at the newly formed Stony Brook University Medical School on invitation of Chairman of Psychiatry Stanley Yolles, the former Director of NIMH. We had met often to discuss cannabis and narcotic antagonist studies. I was pleased to accept his invitation of a tenured research appointment on the Stony Brook faculty with space for my EEG laboratory and a promise to open an ECT Service under my direction at University Hospital when that building was completed. That service opened in 1980 with a 30-bed adult psychiatry unit equipped with a 2-room ECT service. ECT was widely perceived (and is still today) as a treatment especially suited for patients with depressive illnesses, those with melancholia. My psychiatric patients at Hillside and at Gracie Square Hospitals were from the narrow populations that were hospitalized specifically for ECT treatments. Experienced clinicians at GSH had also successfully treated depressed and psychotic patients with diverse medical illnesses in whom ECT was widely discouraged elsewhere, even interdicted, by fears that the electric stimulus would adversely affect the heart and the brain. Induced seizures, especially under modern sessions using sedation, oxygenation, and muscle relaxation are remarkably safe, though.

Now that I was the responsible clinician in the choice of treatments in an academic general hospital I explored ECT in patients with systemic medical disorders and psychiatric symptoms. We successfully treated mentally retarded adolescents, pregnant women, patients with brain tumors, brain aneurysms, and cardiac pacemakers, malignant catatonia, anemia, Parkinsonism, delirium, and pseudodementia.[17] Patients in each of these categories safely tolerated the acute seizure when properly done, despite the popular negative challenging views of "electric shock to the brain."

ECT in Adolescents. The use of ECT for children and adolescents was broadly interdicted by child psychiatrists as a matter of faith. They believed that ECT permanently damaged the developing brain. They did not ask for ECT consultations nor would they consider prescribing psychoactive drugs until the 1990s. Gabrielle Carlson, the Stony Brook Director of Child Psychiatry, would not allow her residents, many of whom had been trained in ECT while on the adult service, to consider ECT in any of their patients. The adult service, however, admitted adolescent patients over age 13. We successfully relieved adolescent patients in delirious mania, suicidal depression, malignant catatonia, and psychosis induced by LSD and

cannabis. Young patients tolerated the treatments easily and the relief of psychosis was rapid with almost all returning home and to school.[18]

Mentally retarded patients are not protected from disorders in mood or psychosis by their condition, but when they suffer such illnesses, ECT is interdicted by beliefs that inducing seizures would further damage their brains. As our experience with adolescents became known, MR patients were referred for treatment and we described positive outcomes with remarkable improvements in their quality of life.[1920]A 14-yr-old mentally retarded boy with persistent self-injurious behavior (SIB), unresponsive to social and medication treatments was referred for treatment, to cite one instance.[21] He was admitted wearing helmet, gloves, and restraints to keep him from injurying his head, accompanied by full-time aides for continuing protection. The referring physician asked whether ECT was an option. With parental consent a trial of ECT was begun. Within two weeks the restraints were no longer needed and he was allowed the freedom of the hospital unit. Over the next half year, continuation ECT sustained him in his community residence without the recurrence of his self-injurious repetitive behaviors. Decades later, Dirk Dhossche, a graduate of the Stony Brook University residency training programs and a participant in the catatonia studies, and Lee Wachtel, Directorof the Neurobehavioral Unit of the Kennedy Krieger Institute of Johns Hopkins University, would identify SIB as a form of catatonia in autism, treatable by ECT.[22]

ECT in Pregnancy. Many clinicians feared ECT during pregnancy, anticipating damage to the fetus by the electric currents and by the mother's seizure, inducing miscarriage. But as fetal malformations were increasingly associated with psychoactive drug use during the first two trimesters of pregnancy, ECT was increasingly ventured. We simultaneously monitored the maternal and the fetal heart rates during each treatment. As the seizure in the mother unfolded, we could hear the rapid increase in her heart rate from 70 bpm to the 110s while that of the fetus ran at its own steady rapid rate of 110 to 130 bpm. The fetal heart rate did not increase during the seizure, showing only a small transient increase during the post-seizure recovery.[23] After more than a dozen such monitored seizures, we no longer requested fetal monitoring and routinely accepted pregnant psychotic patients for ECT. We learned how to treat patients in each pregnancy trimester and optimally position a large pregnancy for proper oxygenation and anesthesia. The benefits of ECT were not limited by pregnancy and is now an accepted treatment.

*Pseudodementia.*Confused elderly patients with poor memory, poor orientation, and poor self-care are considered demented and commonly labeled to be suffering Alzheimer's disease. In some patients, however, the behavior is not the result of a structural brain defect but the consequence of a melancholic depressive illness identified as pseudodementia.[24] Both the mood disorder and the dementia signs disappear with effective antidepressant treatments. All patients admitted to my psychiatric ward labelled as suffering from "dementia" were carefully evaluated and many treated for melancholia.

This lesson was brought home to me by a 58-yr-old depressed, often mute, staring, and posturing woman who had been diagnosed as suffering from Alzheimer's disease at two prior hospital centers. For eight years she had been continuously cared for in her home by her husband and daughters. When Helen was admitted to University Hospital with acute pneumonia, she appeared confused, disoriented, and depressed. A trial of antidepressant medications offered temporary relief but a full course of ECT resolved her dementia. She returned home to care for herself and her family. She relapsed, however, and monthly continuation ECT sustained her for years. Each relapse was marked by mutism, staring and repetitive picking at pictures and wall signs. When these symptoms were recognized as signs of catatonia, treatment with lorazepam extended the periods of her relief and only occasionally was ECT required. She lived for another decade, caring for her home and family, and taking part in community affairs.[25]

As we could not distinguish pseudodementia from a structural dementia by our examinations, we offered medications, especially the older tricyclic antidepressants, finding good relief in about a quarter of the trials. An 85-year-old man with a 2-year progression of dementia requiring continuous nursing care was admitted for evaluation. Among the test findings he exhibited a positive dexamethasone suppression test consistent with melancholic depression. ECT was offered and accepted. Within three weeks he became oriented and able to care for himself. Continuation treatment with imipramine sustained his benefit and on one clinic visit he appeared well-dressed, accompanied by a well-dressed mature woman, declaring that they were to be married that week.

Sadly, in the ensuing years since I left active service the prejudice against ECT is so strong that my recommendation among consultations for senile dementia were frequently rejected. The risks of ECT and of tricyclic antidepressants are small compared to the potential gain to a more normal mature independent life.[26]

Delirium. Many psychiatric consultations in a general hospital are to evaluate delirium, the common confusional and disoriented syndrome associated with systemic diseases, trauma, anesthesia, and surgery. After successfully relieving patients in delirious mania with ECT,[27] we successfully treated deliria in post-surgical patients, those with abnormal systemic hormonal and fluid balances, and in alcohol withdrawal.[28] We often found signs of catatonia in delirious patients, justifying the recommendations for ECT or high doses of benzodiazepines.

Systemic medical risks. Many authors ascribe undue risks for patients with systemic illnesses. Brain lesions, tumors, and vascular abnormalities are considered "absolute contraindications" for ECT on the fear that the seizure would increase cerebrospinal fluid (CSF) pressures leading to cerebellar herniation and death.[29] But the CSF pressures do not rise during our modified treatments. We reported safe treatment in a patient with a growing meningioma[30] and in a patient with a large arteriovenous malformation.[31] Treatment of mentally ill patients in atrial fibrillation found conversion to normal sinus rhythm to occur and led us to recommend ECT with anticoagulation treatment as safe.[32]

Optimizing Treatments. We sought ways to optimize our treatments. The sedation and amnesia associated with the anesthetics etomidate, propofol, and ketamine, which were similar to that of methohexital, sometimes proved valuable. We found a special use for ketamine in delirious patients – an intramuscular injection would sedate a very disturbed patient within a few minutes, allowing us to move the patient from the ward room to the treatment room, and successful treatments followed without need for additional anesthesia. The induced seizures were more robust and their durations longer with ketamine.

Neither etomidate nor propofol offered better amnesia than methohexital. Propofol raised seizure thresholds and shortened the duration of seizures. In elderly patients its use elicited seizures of poor quality. The rise in threshold associated with propofol is useful, however, in treating adolescents since their seizures are often prolonged even at minimal electrical dosing.[33]

We studied the varying durations of monitored seizures by EEG, heart rate, and motor movements. In such recordings EEG durations were generally greater than 40 seconds, and arbitrarily considered "prolonged" when greater than 180 seconds. We often used intravenous diazepam to end seizures that ran over 150 seconds. Measured durations of EEG were longer than that of the motor seizure and both were commonly longer than the duration of the heart rate increase.[34]We augmented seizure duration by injections of theophylline and caffeine. Although

both agents lengthened seizure durations, such use had no observable benefit in treatment outcome and we discarded their use.[35]

How best to select energy to induce an optimal seizure? Concern for the cognitive side effects led to popular use of ever lower energies, just sufficient to elicit a motor seizure, often measured as 10 to 30 seconds. Were these seizures "adequate" for clinical benefit? We evaluated our recordings and identified a pattern of a slow build-up of amplitudes, onset of slow wave bursts mixed with spike activity, sudden ending in an electrically silent period. Seizures less than 40 seconds did not show these characteristics. For a number of years, clinicians were confused about seizure duration and efficacy. Some considered a series of short seizures, with added durations greater than 25 seconds "adequate" but such short seizures were clearly ineffective. Adequate seizures are best defined when greater than 40 seconds in duration with the full elicited EEG pattern. [36]

ECT in schizophrenia. The role of ECT in treating schizophrenia is confusing. Early I used the guidelines for diagnosis that labeled patients who were persistently psychotic, with language and speech abnormalities, episodic excitement and aggressive behavior as meeting the Kraepelinian criteria for schizophrenia that were adopted in the official American Psychiatric Association DSM classifications. We had no test to identify or verify such diagnoses so the treated patients were highly varied. The report of the 1978 APA Task Force on ECT offered little guidance, citing promising reports from clinicians with wide experience and the failure of organized clinical trials.[37] I was invited to write several reviews, each time offering ambivalent opinions in the report.[38] No consensus could be reached because the diagnosis of schizophrenia was itself ambiguous, not distinguishing among long-term, chronic hospitalized patients and short-term acutely ill in ambulatory settings. In 1996 I undertook an detailed review of the published literature, concluding that schizophrenia was not a diagnosis that responded to induced seizures except in cases of catatonia, the syndrome that had erroneously been classified as a schizophrenia type.[39]The review concluded that the types of schizophrenia identified as paranoid, disorganized, undefined, and residual (each best viewed as variations of "hebephrenia") were unresponsive to ECT. The single form of schizophrenia that was responsive was the catatonic. But as defined later, this form was erroneously identified as schizophrenia. (See chapter 8.)

The presence of mood disorder in conjunction with schizophrenia confused the matter. A melancholic psychotic illness is difficult to distinguish from schizophrenia and the insecurity is

commonly arbitrated with the label of "schizo-affective" illness. Except for neurosyphilis, some hormone and vitamin deficiencies, and catatonia and melancholia, psychiatric diagnoses are "in the eye of the beholder" and are not test verifiable. By contrast, the diagnoses of systemic medical illnesses have come to depend more and more on verification tests. The "medical model of diagnosis" is rejected in psychiatry – indeed the DSM classifications specify that no tests are known and none are applicable and that the diagnoses are best made by the association of symptoms recorded in interviews and the illness course. In studies of catatonia and melancholia, my associates and I, however, have argued that the search for verification tests is essential to the development of a psychiatric science. [40]

Clozapine and ECT. At Stony Brook's University Hospital we had often augmented a patient's slow responses to chlorpromazine or fluphenazine with ECT. When clozapine was first tested for the relief of psychosis, it was associated with an acute blood dyscrasia and withdrawn from the formulary. At the behest of clinicians who believed they saw unique beneficial properties in its use, however, prescription of clozapine was reinstated, but limited to patients who had failed at least two prior medication trials and whose blood could be tested weekly. We did not see a particular clinical benefit for clozapine alone in our patients. When we augmented clozapine treatment with ECT, the augmentation was occasionally useful.[41]

Such combined treatment was encouraged by the EEG of clozapine. With clinical doses the EEG pattern becomes filled with bursts of slow waves, and the risk of overt seizures at high dosages. Such physiologic effects justified a clinical trial. We treated psychotic patients with clozapine and then, when the results were poor, augmented the treatment with ECT. We thought the synergy of the two treatments might be clinically useful and considered a proper clinical trial.[42]

The faculty at Hillside Hospital had supported clozapine use in therapy-resistant psychotic patients. Many outpatients, however, were poor clozapine responders and they constituted a large population in their clinic. After I resumed an affiliation with Hillside Hospital in 1997 for the CORE studies I raised the question of augmenting clozapine with ECT. I applied and obtained financial support from NIMH for a random-assignment study of ECT in clozapine treatment failures. Half the patients who had not responded to at least eight weeks of serum-level monitored clozapine treatment continued with ECT augmentation and half continued clozapine alone. A 40% reduction in PANSS positive symptom scores without change in

negative symptoms was recorded in about half the patients. What was missing in this study was treatment by ECT alone after withdrawal of clozapine. Intensive statistical manipulation of the ratings found minimal statistical advantages.[43]

Seizures and brain concentrations of fluphenazine. Was the increase in response of patients whose neuroleptic treatment was augmented by ECT seizures due to elevated brain concentrations of the neuroleptic agent, we wondered? Studies by Tom Bolwig of Copenhagen had reported an increase in permeability of the blood-brain barrier after induced seizures in rats and in humans.[44] We measured the brain concentrations of fluphenazine in rats treated with electroconvulsive shock but were unable to record a difference and discarded this hypothesis. [45]

*Is Isoflurane anesthesia therapy a replacement for ECT?*In the 1980s, Gerhard Langer and his colleague Greta Koinig in Vienna induced repeated sessions of isoflurane anesthesia in depressed patients believing such anesthesia sessions could replace ECT-induced seizures.[46] Isoflurane is an inhalant anesthetic that quickly induces a flat-line EEG with loss of EEG rhythms. Their report that six sessions on alternate days relieved severe depressive illness and was an effective replacement for ECT prompted my visit to the clinic in Vienna in 1983. I observed the feasibility of inducing isoelectric ("flat-line") EEG periods with the anesthetic and decided to replicate this experience.

With the collaboration of Stony Brook anesthesiologists, isoflurane anesthesia sessions were undertaken in six patients who had been readmitted with recurrences of severe depression after earlier successful courses of ECT. In 21 of 26 anesthesia sessions, an isoelectric "flat-line" EEG lasting between 5 and 12 minutes was recorded. We did not observe reductions in depression rating scale scores, nor persistent changes on memory tests, nor characteristic changes in the inter-session EEG. After these failures, the patients were treated with conventional ECT with clinical recovery in five of the six. We did not see isoflurane suppression as an effective alternative for the seizures of ECT.[47] Periodically, this technology prompts interest and is re-evaluated.[48] The studies have been poorly controlled and the report conveys the authors' enthusiasm without evidence of persisting behavioral or physiologic effects.

Continuation ECT

Post-World War II ECT patients had been increasingly treated as outpatients in doctor's offices, both for the treatment courses and continuation treatments. But as ECT use in the 1980s increasingly demanded collaboration of a qualified anesthesiologist, ECT became a hospital-based procedure. The prescription of a fixed number of treatments, usually 6 to 10, became commonplace. Such courses had been sufficient with the high energy, bilateral placement seizure inductions favored by the office practitioners. When patients showed signs of relapse, ambulatory continuation treatments were readily undertaken. During the 1970s, with repeated public and professional attacks on ECT, physicians often negotiated a fixed number of treatments for a course. The idea that the length and frequency of an ECT course could be prescribed in advance, even agreed to in the patient-signed printed consent, was widely accepted. The treatment image became one of a specifically effective treatment, much like a prescribed antibiotic for an infection. But ECT treatment for depression or mania or even catatonia is more like that of insulin for diabetes: an acute fixed schedule is prescribed and is immediately effective but open-ended continuation dosing is necessary for sustained relief.

When ECT was re-introduced in the 1980s, many thought that psychoactive medications would sustain ECT relief. After a course of ECT patients were prescribed psychoactive medications, often in unique combinations of polypharmacy, and while success was common, relapse became an increasing burden.

In 1987, Thomas Aronson and colleagues from the Stony Brook out-patient treatment facility reported greater than 50% relapse rates within 6 months for my ECT-treated delusional depressed patients regardless of continued medications.[49] I was chagrined and saw the need for continuation ECT. Our ECT Service treated patients three days a week, so we set aside one day (and later two) for out-patient treatments. We no longer asked patients to consent to a fixed number of treatments but asked their consent for continued observation and treatment "as needed" beginning as in-patients and continuing in our ECT out-patient clinic for six or more months.

How best to prescribe and manage continuation treatments was widely discussed in the journal *Convulsive Therapy* and at meetings of the Association for Convulsive Therapy (ACT). That Association established a Task Force that surveyed usage, evaluated risks, and

recommended guidelines, publishing their conclusions in 1996. I chaired the group and published a report that became a guide for continuation treatments. [50]

The CORE Study.

In 1992 Harold Sackeim of Columbia University applied for NIMH support for a multi-site study of continuation medications – placebo, nortriptyline, and the combination nortriptyline and lithium -- after ECT among unipolar major depressed patients. The NIMH consultants reviewing the application asked why he did not consider continuation ECT instead of placebo, since high relapse rates with no continuation medication were well documented. He demurred insisting on the placebo treatment arm.[51] The reviewers, however, were unwilling to support such a study of continuation medications alone. The chairman Jonathan O. Cole argued for support, however, agreed to by the members provided a parallel study could be developed comparing continuation ECT with continuation medication of combined lithium and nortriptyline.

With Cole's encouragement I enticed Charles Kellner (Medical University, Charleston SC), Teresa Rummans (Mayo Clinic, Rochester MN) and John Rush (University of Texas, Dallas TX) to collaborate in a multisite collaborative study with the criteria for selection of patients, outcome evaluations, and combined medications identical to Sackeim's Columbia University Consortium study.[52] The single distinction was in the CORE use of bilateral electrode placements at a minimum of 1.5 times the measured seizure threshold while Sackeim's group used unilateral electrode placements with dosing set at 1.5 to 2.5 times the measured seizure threshold in their treatments.[5354]

Patients meeting the clinical criteria for *unipolar depressed patients* were to be identified by an interview with a trained social worker using questions from a standard behavior rating scale. Initially, patients labeled *bipolar depressed* were excluded from the study data but many were treated with the same protocol after rejection from the study. The outcomes of the two subtypes did not differ, so we designed a second study treating both unipolar and bipolar depressed patients randomly assigned to bitemporal, bifrontal, and right unilateral placements. Both CORE studies were funded in 1997 by NIMH.

I was unable to undertake the study at Stony Brook. My funding request to the NIMH assigned some activities to Stony Brook Department personnel. In the four years between the

initial request and its approval in 1997, cuts in the New York State budget had severely affected the university and hospital. When I enquired for release time of personnel for the study, the department chairman, the dean, and the Vice-President each denied my request.

I called John Kane, the director of Hillside Hospital and asked whether I could move the study to his center. After meeting with my Stony Brook colleague Georgios Petrides, Kane accepted the study request and appointed Petrides and me to the Hillside hospital staff. The funding transfer was approved by NIMH and by 1997, the methods of patient selection, documentation, rating scales, and treatment protocols were established.

I retired from Stony Brook in 1997 and established an office at Hillside Hospital in conjunction with the CORE study. In succeeding months Petrides became increasingly responsible for the study and replaced me as the Principal Investigator, allowing me to spend more time at home. I remained active in the CORE study, however, writing many of its reports and attending all its team meetings. During the 14-year course of the CORE study, 19 reports were published. Patient samples were large, among the largest for published ECT studies. As the reports were widely scattered I summarized the experience in 2014.[55]

In Sackeim's CUC study the six-month relapse rates were much as anticipated: 80% for placebo, 62% for nortriptyline alone, and 36% for the combined lithium and nortriptyline. In the CORE study, the relapse rate for lithium-nortriptyline was 39%. With Continuation-ECT 32% relapsed, 22% dropped out of the study, and 46% continued in 6-month remission. We were disappointed with these ECT results and realized that the C-ECT treatment schedule had been arbitrarily set, less effective than what clinicians reported as necessary in ambulatory treatment schedules.[56] When patients relapsed and we were able to induce seizures on clinical criteria alone, almost all patients sustained their remission with ECT as needed, like the treatment of diabetes or heart failure. To sustain an ECT benefit we needed to be flexible and introduce treatments when symptoms recurred. This lesson had been learned by practitioners in the early decades of ECT practice; and summarized in the review by the 1996 ACT ECT Task Force. We foolishly erred in the CORE study based on our desire to be comparable to the CUC study.

Much was learned, however. Seizures induced with unilateral electrode placements (RUL) are inherently inefficient. The lesser immediate (and transient) memory-loss effects associated with a unilateral electrode are a poor justification for outcome inefficiencies and the

increase in the number of seizures and anesthesia sessions.[57] The benefits of bifrontal ECT are slightly inferior to bitemporal ECT but can be justified by their ease of application.

ECT is as effective in patients with bipolar depression as in unipolar.[58] The common belief that ECT is less effective in bipolar depressed patients is false, a consequence I believe of the pharmaceutical industry's drive to establish a place for "mood stabilizers" and anticonvulsants separate from the prescription of lithium and antidepressants in psychiatric disorders, and the unwillingness of the research leaders to recognize ECT as an effective and safe treatment.[59]

ECT rapidly reduces suicide preoccupations in melancholic and delusional depressive illnesses. In the more severely ill, those with high ratings on suicide assessment (item 3) in the $HAMD_{24}$ rating scale, the suicidal self assessments were reduced by 60% with six treatments within two weeks, justifying ECT as the primary treatment in patients who require special protections for suicide risk.[60]

The presence of delusions in patients with major depressions identify a population of ECT-sensitive patients with excellent prognosis for successful ECT treatment. In the 1970s, Alexander (Sandy) Glassman and his colleagues at Columbia University reported that delusional depression did not respond to blood-level, monitored imipramine. They did respond to ECT, however.[61] While the overall ECT remission rate for the major depressed in the CORE study was 84%, the rate among the psychotic depressed patients was much higher, at 95%. The common policy of first treating psychotic depressed patients with medications, especially the use of less effective serotonin targeted antidepressants, with or without atypical antipsychotic drugs, cannot be justified. Like the use of RUL treatments, the insistence that psychotic depressed patients be subjected to one or two medication trials before ECT is questionable as to its efficacy as well as its ethics.

We confirmed again the widespread clinical experience that ECT is more effective in elderly than in younger patients. But this expectation is modified by the surprising efficacy of ECT in adolescents, an awareness not tested in our study but one that has come to the fore as clinicians have become free to treat more adolescents.

05 Electroshock in the Public Eye

I have described studies of the convulsive therapies at Hillside Hospital in the 1950s, the inquiry by Richard Abrams that led to our studies at Gracie Square Hospital in the 1960s, clinical studies in the 1980s and 1990s as an Attending Psychiatrist on the in-patient Service at Stony Brook University Hospital, concluding with the 4-hospital CORE collaborative studies at the Hillside Hospital from 1997 until my retirement in 2005. Not only my active research and clinical work, but even more, my presentations at professional meetings and hundreds of publications over the decades made me internationally known as a "defender of electroshock."[1]

The public and professional references and images of electroshock, especially beginning in the 1970s, were commonly negative and I have often thought that I would have been happier if I had put these interests aside. For the patients who responded to treatment, though, the benefits were often life-saving and for the treating physicians rewarding and reassuring that I continued both the studies and the clinical care. The science of the treatment's mechanism of action has been a continuing academic challenge. Nevertheless, for many life-altering behaviors and systemic disorders, inducing seizures offers greater relief with greater safety than the plethora of pills, imaginative psychotherapies, and scalp tickling magnetic and electric neurostimulations that dominate today's psychiatric practice. The prejudices against ECT remain widespread within the medical and the public communities.

Was the mark of Cain that prejudices its use deserved by the discovery that inducing seizures relieved psychiatric illnesses? The carnage of the First World War released unhuman attitudes and tolerance, even enthusiasm, for attacks on human bodies in the name of treating the severe psychiatric ill. Prolonged sleep for days on end was accompanied by pneumonia and death; comas and seizures induced by insulin led to prolonged coma and death; lobotomy, especially the ice-pick variety, was associated with seizures, hemiplegia, and death.[2] Although electroshock had none of these risks, it was lumped together since the practitioners of one were called upon for all.[3]

The first inductions of seizures by chemicals did not go well. Ladislas Meduna, at a state hospital in Budapest, induced seizures by injecting the irritant camphor-in-oil into patient muscles. Few injections resulted in a seizure, all were painful and irritated the tissues. He next tested the intravenous chemical pentylenetetrazol (Metrazol), which, although more efficient, failed often enough that patients became extremely anxious, frightened, and refused further

treatment after experiencing a panic induced by a partial seizure. Despite panic and pain, the relief occasioned by many of the first patients encouraged its continued use.[4]

In May 1938 two Roman physicians, Luigi Bini and Ugo Cerletti, devised a more assured and less frightening method using electricity that quickly replaced chemical inductions and has since been the standard method of inducing seizures worldwide. Although the inductions were still frightening to both patients and clinicians, they aroused little public concern. They were better accepted within medical practice, and less feared than insulin-induced comas, prolonged sleep, or leucotomy.

The names "electroshock" and "shock therapy" added to public concerns but did not stop the practice.[5] That the treatment relieved the suicidal depressed, the hopelessly psychotic, and the uncontrollable manic encouraged widespread use in the world's sanitaria and physicians' offices. This success occurred at the time when the leaders of psychiatry were enthusiastically following the flag of psychoanalysis, promising cures for the psychiatric ill after months and years of "talk therapy" catering to the walking wounded. Psychiatric leaders committed themselves to the psychology of the mind, separate from the functions of the body and the brain.[6] Every report of relief of an emotional disorder by fits and the repeated highlight of another Freudian therapy had failed or required a new therapist stimulated defensive attacks by psychiatry's leaders that electroshock did not help the patient "understand or resolve his conflicts." The benefits of inducing seizures were considered transient and, furthermore, damaging to the brain and antithetic to psychoanalysis since seizures extinguished personal memories.

Immediately after the end of World War II, American psychiatric leaders formed a select political society, the *Group for the Advancement of Psychiatry*, that issued its first broadside on "Shock Therapy" on September 15, 1947.[7] The handbill complained that electroshock's widespread use in office practices offered only temporary relief. The benefit was considered inferior to the psychoanalytic understanding of life's experiences and the resolution of conflicts that were the supposed basis for a patient's distress. I had studied psychodynamic theory at New York's William Alanson White Institute and had undertaken a personal analysis for five years. I saw no challenge to a "biological explanation" of a patient's history and symptoms and the reality that "somatic" treatments relieved my patients. No matter how I presented my experiences of rapid relief induced by repeated seizures, I was met by disbelief. When, in the

1970s, it became fashionable for Hollywood and Broadway to romanticize Freud, the romanticism was accompanied by images of Frankenstein's monster, the electrified man, as the frightening alternative.

Public reports of an excessive use of ECT in children in Massachusetts in 1970 sharpened the attacks. State legislators frantically proposed laws to prohibit ECT. Milton Greenblatt, the director of the state's mental health program, argued that legislative restrictions would interfere with accepted medical practice and negotiated the tabling of the proposed legislative bills until the actual experiences could be studied. He commissioned a survey of ECT in Massachusetts to be conducted by Fred H. Frankel, Professor of Psychiatry at Boston's Beth Israel Hospital and an expert in hypnosis treatments.[8]

The 1973 review of practices in Massachusetts did find hospitals where ECT use was excessive in numbers of treatments, the methods of seizure induction haphazard, and medical care facilities inadequate. Greenblatt issued medical guidelines to standardize ECT practice. His report and the regulations satisfied both the legislature leaders and the practitioners, markedly improving clinical practice, becoming a national model for treatment facilities. The resolution encouraged a broader acceptance of the treatment and a reference source for establishing treatment facilities.

First American Psychiatric Association ECT Task Force(1975)

Early in my career in psychiatry, at annual meetings of the American Psychiatric Association (APA) I joined the Section on Brain Function & Behavior where ongoing arguments on how to optimize induced seizures were active.[9] Discussions on ECT were also featured as clinicians assembled annually at the Electroshock Research Association, Society of Biological Psychiatry, and similar associations dedicated to lobotomy, insulin coma, and carbon dioxide therapy. When Milton Greenblatt deflected the drive of the Massachusetts legislature in 1970 to interdict the use of ECT, he organized the survey of ECT and also asked me to edit a special number of his journal *Seminars in Psychiatry* on the scientific status of ECT.[10]

Legislative restrictions against the use of ECT and lobotomy with specific interdiction in persons under age 18 surfaced again in 1972, this time in California. In response, psychiatrists led by Dr. Gary Aden applied for court relief from legislative interference in medical practice.[11] The court agreed that legislative restrictions of medical practice were unacceptable. The

legislature responded by using the state's power to monitor health and safety to limit the number and frequency of treatments, restrict guidelines for consent, require extensive reporting of treatments, and prohibit its use in persons under the age of 18. The regulations forced many patients in need of treatment to go out of state as California physicians abandoned the treatment.[12] These regulations are still in effect in 2017 and have severely limited ECT use, especially in adolescents. The same restrictions were adopted in Texas in 1993 and in other states to a lesser degree.[13]

Requests for professional support by California psychiatrists led the American Psychiatric Association to establish a Task Force on ECT in 1975, and appointed Fred Frankel of Boston as its chairman.[14] I was an appointed member. The report published in May 1978 described whom to treat, how to assure safe procedures and effective treatments, and discussed concerns about cognition and memory and how to minimize these effects.[15]

A query about ECT practices had been sent to 20% of the Association's membership. Responses were received from 75% of those canvassed. Was ECT an appropriate treatment for any of 11 different psychiatric diagnoses? The responses showed widespread confusion as to whom to treat. ECT was considered useful for patients with major depression (86%), less so for manic excitement (42%), and marginally for schizophrenia (25%). About 22% of the responding practitioners had used or recommended ECT in the prior 6 months. Featured in this confusion was the inadequacy of the official psychiatric classification schemes, their use providing poor descriptions and inadequate diagnoses and not assuring optimized treatment plans.[16]

The Task Force members were experienced in clinical care and most procedural questions were readily resolved. A thorny issue was endorsement of treatments using unilateral electrode placement. In studies at Gracie Square Hospital we had found such treatments inefficient compared to treatments using bilateral electrode placements.[17] Lesser complaints of recall and orientation immediately after the seizure with unilateral electrodes encouraged some practitioners to endorse its use. At a committee vote, I and another clinician member could not recommend the use of unilateral placement, arguing that its inefficacy necessarily led to increased numbers of seizures with attendant anesthesia risks, lengthened hospital stays, higher costs, and potential for increased mortality.[18] The reported lesser effect on cognition was transient, not justifying the inefficacy of the treatments and prolongation of illness.

When the Task Force report was submitted to the APA Board of Trustees for publication under its imprimatur, the policy leaders insisted nevertheless that the unilateral form of treatment be endorsed (along, of course, with the bilateral form), to support the practices and beliefs of some members.

How best to assure consent? Patients referred for ECT are the more seriously ill depressed, psychotic, delirious, and suicidal, often mute and negativistic, raising questions as to their competency to understand the risks and benefits of proposed treatments and to consent freely. Can a patient so ill as to be referred for seizure therapy properly evaluate the risks of memory losses described by psychologists and in the public press? Medical practice treats patients by voluntary consent, the patient appearing at the physician's office and choosing whether to follow the physician's prescriptions. Can the same rules apply for electroshock?

The Task Force members recommended a lengthy printed description of the procedure with detailed risks to be read by and to each patient, to be signed voluntarily by the patient, and properly witnessed. The form would name the responsible personnel, and specify the maximum number of treatments under the consent.

I was conflicted in this discussion. My father was a general medical practitioner; I had seen his interactions with patients and their families, and how they respected him and readily accepted his recommendations, including his insistence for an independent second opinion in complex diagnoses. I experienced the same deference when I took over his practice during his holidays and again when I opened a community office in Great Neck for consultations in neurology and psychiatry. In the Task Force discussions, I was one of two physicians who, at first, did not see the need for a written "contract" but I did endorse the consent procedure.[19]

ECT was viewed as a surgical procedure (since it uses anesthesia) with a potential for harm that must be consented to by the patient. Patient autonomy would be respected by describing the anticipated benefits and risks before treatment and treating only those who voluntarily agreed. Further protection was to be achieved by a family member also reading the descriptions, discussing the procedures and risks, and witnessing the patient's signature.

Exceptions to voluntary consent were recommended for those with mental deficiency or dementia, who were considered to be within family and community responsibility. State-mandated procedures for judicial authorization for treatment on an incompetent patient's behalf were supported by the task force.[20]

The recommendation of a signed, voluntary consent for treatment was the main benefit of the Task Force Report. The text was considered an "official" action of a national association and served as a guide for the opening of new ECT treatment centers throughout the nation in the post-1978 years. I was often invited to visit and organize new treatment units based on the Task Force Report. The recommended procedures were sufficiently conservative to be widely adopted.

The Task Force report was distributed at the May 1978 APA annual meeting in Miami with each task force member presenting an aspect of the report to a large audience. I was the spokesperson for the technical recommendations. The report was generally accepted and praised. The concept of a writtern consent was argued but accepted. The note accepting treatments through unilateral placements, however, met strong protests from practitioners, notably New York's Lothar Kalinowsky. Much of his criticism was directed at me as the spokesperson. These practitioners, themselves extremely well experienced with bilateral and unilateral electrode placements, argued that treatments through unilateral electrode placements were so inefficient as to put patients at risk of prolonged illness and suicide, poor outcomes, longer courses of treatments, and higher relapse rates.[21]

Electrode Placement, Memory and ECT

The argument persists, however, encouraged by the constant singing of a "memory loss" mantra by the psychologist Harold Sackeim and his colleagues and by leaders of the ISEN, the International Society for ECT and Neurostimulation, the present professional organization supporting ECT use. At this writing, more than half a century after the initial studies, the use of unilateral electrode placement persists despite compelling evidence of its lesser efficacy in the studies sponsored in the UK in the 1960s [22] and the more extensive NIMH-supported studies by the Columbia University Consortium (CUC) and the 4-hospital Consortium for ECT (CORE) that clearly showed that seizures induced through unilateral electrodes were clinically less effective, lowered recovery rates by 40% and increased the mean number of treatment sessions from 7 to 10.5.[23] Physicians knowingly offering patients lesser effective treatments that increase risks of treatment failure and higher relapse rates are unethical.[24]

What is the impact of ECT on memory? Patients who come to this treatment are severely ill, often with long periods of poor self-care, poor sleep, and preoccupation with the self, the

body's discomforts, and little attention to work or family. They are then advised that they will need anesthesia, and electricity will course through their heads and brains. They are warned, verified by the consent that they (and often members of their family) are asked to read and sign that explicitly states that they may lose memory, become confused and disorientated. They are then given a chemical intravenously that puts them to sleep, electrodes are pasted on the scalp and head, and a grand mal seizure is induced.

Every seizure disrupts the brain's physiology and chemistry. Awakening is slow, with confusion and disorientation persisting for some minutes in all subjects, much longer in the elderly and brain compromised. Most patients since the 1960s have first been treated with brain poisons – every "psychoactive" pill, whether antidepressant, anxiolytic, or neuroleptic or whether the alcohols, marijuanas, opioids or sedatives that are publicly attractive -- each induces persistent changes in the brain's electrophysiology that is measurable by the EEG. Responses to questions in the first hours after a treatment are slow, deliberate, and confused. And, it is fashionable nowadays, and surely by the psychologists and nurses who test for memory effects, to fire questions, one after another before treatment and again as soon as the patient's eyes are open.

Where are you?

What is my name? What is your name? Where do you live?

How much is 23 times 11? What is today's date? Who is the President?

And on, and on.

When tests are repeated after many hours, the answers are slow and now correct. But after a series of treatments the errors may persist for days, especially in the elderly and in the chronically ill who have been the most brain-poisoned by an extensive potpourri of medicines.

When specific neuropsychological tests are done before treatment and again a week, a month, and 6 months after the last treatment, the recovery of cognitive functions is progressive so that in time the recovered patient functions as well or better than before the illness. In batteries of more than 20 tests, psychologists have generally found that the normal functions have returned with only some personal memories still offering errors. Of course, the psychologists Harold Sackeim and Larry Squire have focused attention on these singular test data, not relating their test measures with the clinical changes in the patients.

I have repeated psychological testing in all my ECT studies, at Hillside (twice), New York Medical College, and Stony Brook. I am often surprised by the quick return of functions with recovery after the illness. In the elderly I am not surprised by the patients who, in the hours after a treatment, speak poorly, recognize a relative hesitantly, and soil their beds. For the many who recover, these deficits disappear, and the patients return to pre-illness activities. Patients and family members are satisfied; so much so, that they insist on ECT when the illness recurs.

Slow recovery is common in the repair of any illness. Think of the pains and discomforts in the long rehabilitations after a fracture, after major surgery, after acute trauma. The recovery after a course of electroshock is the same slow and repair quality of major surgery. Shouting "memory loss, memory loss" is the same as shouting "painful walking, painful walking" after hip surgery.

What is to be made of the anti-ECT positions of psychologists, psychiatrists and psychotherapists? The slander that has infected ECT from the immediate post World War II period persists and frightens practitioners so that they do not realize that by offering inadequate treatments they are encouraging ongoing negative attitudes. The enthusiasm of the ECT practitioners for non-seizure treatments and the scalp tickling of the "brain stimulation"movements (encouraged by payments by industrial concerns) thrives on the falsehood that these treatments "do not affect memory." Yes, they do not affect memory functions, but they also do not relieve the melancholia, catatonia, mania and delirium that follows with proper ECT.

My personal studies of the effects of induced seizures on cognitive functions are detailed in my 1979 textbook, and my 2014 summary of my CORE studies, reporting that the memory effects are transient and no more limiting than the pains and blood loss after surgery. The most realistic and best documented reviews of the cognitive data are to be found in Abrams' textbooks.[25]

***Convulsive Therapy:* The Textbook**.

I was unhappy with my acquiescent vote in the Task Force report. I had already tested the scientific question on optimizing treatments and unilateral electrode placement and my conclusions had been verified by well-designed studies by others. I had induced seizures using currents from different devices and the chemicals flurothyl and pentylenetetrazol; had tested

various sedatives and muscle relaxants to sedate patients; had measured changes in brain and body physiology and overseen numerous neuropsychological tests; and had broadened my experience to treat patients with systemic and behavior syndromes beyond schizophrenia and depression. I decided to spend a sabbatical year to review my research experience and the experimental ECT literature and write a textbook focused on the experimental evidence.

My text described Meduna's first experimentswith seizures and the changes in body and brain physiology and reported our studies of electrophysiology, neuropsychology, and language and discussed the many theories of mechanism. A manual of practice for safe and effective treatment and an extensive citation of the literature ended the volume.

The book was published in 1979 by Alan Edelson of Raven Press, a publisher of neuroscience.[26] It appeared at a moment when the future for psychopharmacology appeared unlimited and that of convulsive therapy bleak. Inducing seizures had been shown to relieve melancholia and mania, but interest was overshadowed by the unbridled enthusiasm for psychoactive drugs.[27]

***Convulsive Therapy:* The Journal**.

I also launched a quarterly scientific journal dedicated to the treatment. In 1984 I was invited by Ole Rafaelson of Copenhagen to discuss electroshock in a plenary session of the summer bienniel meeting of the CINP – the international society of psychopharmacologists in Florence. I challenged the members to recognize the induction of seizures as an effective way to change brain chemistry, and thus was as much a form of psychopharmacology as prescribing pills and potions. I urged the inclusion of electroshock treatments in their list of potent treatments, and urged comparisons of medications and induced seizures in controlled studies to improve methods for therapeutically altering brain chemistry. Alas, my message was ignored. None of the members, nor any psychopharmacologists, nor any research funding source, nor any government agency has considered inducing seizures with the enthusiasm or interest in psychoactive drugs that are internationally marketed.[28]

After the lecture Martha and I were invited to dinner by Alan Edelson. Would I consider editing a journal under his flag, on a topic of my choice? We discussed the merits of the disciplines of convulsive therapy and pharmaco-electroencephalography, two disciplines that lacked a journal, and both of interest to me. Later that year I met Alan for lunch in New York

City and over dessert he brought out a publisher's contract for a quarterly publication with the title blank. I entered the title *Convulsive Therapy* and signed.

After canvassing my colleagues and friends for an Editorial Board and initial submissions, I compiled sufficient edited material for the first number to appear in May 1985. In addition to a variety of topics on convulsive therapy I was particularly pleased to publish the autobiography of Ladislas Meduna, the discoverer of induced seizures as treatments, in the first two issues.[29] I had tracked the typescript to the offices of Dr. Abraham I. Jackman that Meduna had shared in Chicago in his clinical practice, edited the typescript, and published the autobiography.

The Journal's emphasis was on clinical issues in safe and effective treatments.[30] Every issue cited publications on ECT that had appeared in diverse journals. Special numbers in 1988 celebrated the 50th anniversary of electricity in seizure induction and in 1989 discussed theories of seizure mechanisms and benefits. Book reviews and editorials on active clinical issues, safety, and ECT training were invited as well as discussions of new equipment. Over the next decade the journal appeared regularly and on time.

To establish a subscription base, we offered the journal as the official publication of the Association for Convulsive Therapy.[31] In addition I sought advertising support from the ECT device manufacturers MECTA, Somatics, Medcraft, and ElCoT. Each advertised in the journal, though in later years, ElCoT and Medcraft discontinued the manufacture of their devices in the US and pulled out.

I managed the journal for a decade and then turned it over to Charles Kellner, followed a decade later by W. Vaughn McCall. With volume 14 in 1998, the journal title was changed to *Journal of ECT* and added attention to brain stimulation therapies. I opposed this change recognizing that the central event is the grand mal seizure and that no amount of brain tickling by magnetic or electrical currents could be clinically effective in the absence of an induced seizure.[32]

As another educational endeavor in the mid-1980s, soon after the inauguration of the journal I encouraged the development of an informational videotape that would show patients before and after treatment and the actual treatment to assure the needed information was given the patient and the family for "informed consent."[33] With the financial support of Richard Abrams and Conrad Swartz ofSomatics Inc, the 22-minute videotape was made by Richard

D'Alli at Stony Brook's University Hospital.[34] The videotape is stll in use in many ECT facilities.

Second APA Task Force on ECT (1990)

Voices hostile to electroshock became progressively so shrill that the National Institute of Mental Health organized a public Consensus Development Conference on the subject in 1985.[35] Two days of noisome hearings considered the efficacy and safety of the treatments, the beliefs that inducing seizures caused severe memory loss and permanent brain damage, the reasons for and practices of involuntary treatments, the known indications, and the need for more treatment facilities. After extensive emotional heat and much intemperate shouting, the panelists were unwilling to assert the efficacy, safety, and specificity of the treatments. Instead, they called for another survey of usage, cited the need for studies of mechanism and long-term effects, and encouraged resolution of the unilateral and bilateral electrode placement controversy. In response, the American Psychiatric Association established a second Task Force on ECT in 1987 with five clinician members including myself.[36] Recognizing the shift of treatments from office to hospital settings, we recommended better training of practitioners and guidelines for privileging. A requirement for individual and witnessed signed consent, and treatments with unilateral as well as bilateral electrode placements were again endorsed.

Very few residency training centers taught practitioners how to optimize ECT treatments. I decided to establish a training program to certify residents for privileging in ECT. In 1991 at Stony Brook, I organized a one-day certificated educational program for small groups of physicians. I was disappointed when I realized that the technical issues inherent in carrying out actual treatments could not be learned in a single day. Although these sessions were well subscribed, when I moved to LIJ-Hillside with the CORE study in 1997, I organized a 5-day "hands-on" course that has attracted students from many countries and as of this writing is still ongoing.[37] Student groups up to four spend their mornings treating patients, and their afternoons in didactic conferences on a variety of related subjects including viewing videotapes to educate patients for consent.

Convulsive Therapy: The Website

As an offshoot of my interest in education and the expanding ECT literature I created an internet blog website in 1999, www.electroshock.org. Presentations at meetings, book reviews, and citations of newly published reports appeared in each monthly issue. The count of "hits" rose steadily to hundreds a month. While some queries were about the content, more were complaints about treatment failures of ECT. After two years I recognized that literature searches were better done by the newly established National Library of Medicine's *MEDLINE* (PubMed) and that books were effectively reviewed in *JECT*, so I closed the website.

The Stigma Persists: The Challenge of Anti-Psychiatry

The popularity of psychotherapy and psychotropic drugs in the 1960s led to a sharp decline in ECT use. But as medication treatments increasingly failed and families asked what else could be done, ECT use resurfaced. The shadow of lobotomy and patient complaints of memory loss encouraged persistent attacks against ECT, and as these became more strident, my public support for the procedure brought me much public criticism. Burton Roueche's exaggerated description of a government economist's memory loss in the 1974 *New Yorker* article "All About Eve" brought Marilyn Rice to public attention.[38] She instituted a malpractice suit against the psychiatrist who administered the treatments complaining that she had not been warned that her memory would be destroyed and that she would be unable to work. She went on to develop and lead the public action group *Committee for Truth in Psychiatry* that launched further attacks on ECT. She frequently appeared at public forums to challenge ECT use, proclaiming her persisting loss of memories.[39]

After Marilyn Rice died in 1992 the Committee for Truth in Psychiatry was led by Linda Andre, who made the same claims after her treatment course following a suicide attempt by drug overdose. She was a vivacious, well spoken, and attractively dressed woman who attended public meetings and paid particular attention to meetings in which I presented my work. She challenged speakers and attended the 1992 international ECT meeting in Graz, Austria to voice her opposition to the treatment. The international audience was surprised by her personal attacks. She attended my public lectures and protested my presentations at annual Continuing Medical Education psychiatry training sessions in various cities.[40]On one occasion, when the floor was opened to questions, she attacked me as dishonest and paid to lie about the effects of

ECT. She walked up to the podium offering me a tray containing a pig's head surrounded by dollar bills.[41]

Church of Scientologyand Malpractice Defense.

In the 1960s, the national political and social movement headed by the futurist Ron Hubbard opportunistically attacked psychiatry with special attention to the prescription of psychotropic drugs in children and adolescents and the brain effects of ECT and lobotomy. The members and their children demonstrated with shouts and anti-ECT posters in the halls and at entrances to American Psychiatric Association meetings and other sessions at which ECT was discussed. On occasions when its members arranged for complaints to be aired on TV talk shows, I was asked to defend the treatment but refused to take part. The hosts delighted in challenging professionals on their incomes and on the damage that had been done to the patients who complained bitterly about memory losses. Yet, many patients spoke well, encouraged by the host whose mission was to support the "poor" patient and to castigate physicians for damaging patient's brains.

The Church of Scientology also encouraged and financed malpractice suits against practitioners, asserting that patients had lost memories of long periods of their lives, particularly the most personal family memories. I appeared as a witness for the defense on numerous occasions with Peter Breggin, John Friedberg, and Harold Sackeim as expert witnesses for the plaintiffs.

The cases were weak and my defense of the practitioners was successful in every instance except that of Peggy Salters in South Carolina in 2005.[42] She had been given ECT as an outpatient with 13 treatments in 19 days. The physician deemed the patient severely suicidal, justifying the almost daily treatments, but failed to offer her hospital protection. She complained that her memory was so damaged that she could no longer work. My testimony was limited to my experience with intensive ECT and with the experimental procedure of multiple monitored ECT (administering 4 to 6 seizures in one anesthesia session), stating that even these more intensive treatments were not associated with persistent cognitive defects or evidence of brain damage. In this instance, while I did not believe that the patient had suffered reimbursable damage, the physicians had not followed standard practice in protecting the suicidal patient nor in justifying almost daily treatments. I deem the judgment for the patient correct.[43]

BBC-PBS Madness with Jonathan Miller.

In 1990 I received a call from a London TV production company asking if I would help with the presentation of convulsive therapy in a planned 5-hour BBC/PBS documentary on the history of treatments of the mentally ill to be titled *Museums of Madness*. The producer, Jonathan Miller, had impressive qualifications as a Cambridge University graduate in neurology and the son of a psychiatrist. He had acted in the original cast of the successful Broadway play *Beyond the Fringe* (1960-64), directed performances in theatre and opera, and written and directed a popular 13-hour BBC production *The Body in Question* (1979). While playing on Broadway he attended Saturday morning Grand Rounds in Neurology at the Neurological Institute with H. Houston Merritt.[44]

I met with Miller and Grace Kitto of Brook Productions and agreed to their filming of my patients and the treatment procedures at University Hospital. I asked that they return again three weeks after the first filming to record the patient's progress and that I see the frames of my patients before they were aired.

For filming on May 17, 1990 I selected patients with different diagnoses who were early in their course of treatment. SK, an 18-year old delusional psychotic man who had been in repeated treatments for more than two years; EF, a 60-year old psychotic depressed woman who was posturing, repetitive in speech, and unable to care for herself; ET, a melancholic depressed woman with a history of mania and excitement; and JF, an elderly man who had been depressed, lost much weight, and careless in his self-care. Appropriate consent for filming was obtained for each patient. The filming of interviews and treatments went smoothly.

The team returned three weeks later for follow-up filming. Patient SK was better oriented, EF answered questions without repetitive speech or acts, ET smiled and was friendly and better oriented, while JF assured us that while he could not recall why he was being treated, he felt well and was ready to go home. Asked about memory, he thought that his memory was as good as it ever was. The treatments were not painful at all, he said, and surely less uncomfortable than seeing the dentist.

On October 15, 1990 on my way back from meetings in Berlin, I visited the Brook Production Studios in London to review the print. The presentation of the patients and the

treatment were very well done and I was pleased. My concept of neuroendocrine dysfunction as the basis for the disorders that are relieved by seizures was well presented.

Many months later, when the series was aired in the U.S., Miller's voice-over set a very different tone.[45]

'*The administration of an electric shock through the skull is a comparatively crude assault on the brain.*

'. . . as machines were invented to whirl, swirl, shock, rock, and douche the patient back to sanity, the sick brain was treated to a series of traumatic assaults presumably in the hope that its distorted parts would be jolted into place.

'. . . the treatments resulted in violent convulsions with serious bruising . . . fractures of limbs and spine . . . and other atrocious consequences.

'. . . despite its understandably sinister reputation, ECT, Metrazole and insulin have much more in common with the whirling chairs and rotating cradles which they superseded, in that they were addressed to the brain as if it were a single undifferentiated organ."

Miller's failure to find a positive thread in the histories presented by the patients left many viewers with a bad taste, and the series was not presented again. In a recent biography of Miller, the author Kate Bassett makes much of Miller's conflicts with his father, a leading forensic paychiatrist, as the basis for his negative attitude to medicine.[46] Whether this relationship contributed to his views of psychiatry or not, he was among many creative writers who saw psychotherapy and psychoanalysis favorably, indulged in by themselves, friends and family members, with medicines and electroshock treatments as hazardous, ineffective, and not acceptable in their social class.

***A Beautiful Mind:* The Nobelist John Nash and Insulin Coma**.

A call from the biographer Sylvia Nasar in 2001 asking whether I had experience with insulin coma therapy made me aware of the life history of the 1994 Nobelist in Economics, John Nash. A brilliant mathematician, Nash had successfully completed his doctorate at Princeton University, publishing a thesis on game theory that was reputed to revolutionize economics. While teaching at MIT in May 1959 he became delusional, overactive, impulsive, and fearful, meeting criteria for delirious mania. He was treated in Boston's McLean Hospital by

psychotherapy and chlorpromazine. Aware that his statements led to his incarceration he hid his beliefs and was discharged to the community. He left his teaching position and returned to Princeton.

The paranoid psychosis persisted and he fled to Europe and sought to give up his American citizenship. Returning to Princeton in 1971 floridly delusional, he was admitted to Trenton State Hospital. His Princeton colleagues implored the Medical Director that Nash was a potential Nobelist and warranted the most effective treatment. Insulin coma treatment, although discarded elsewhere, was still in use. It was the most heavily staffed service, and in response to his colleagues' pleas, Nash was assigned for treatment in that unit. He responded by relief of his overt delusions but the director suggested the follow-up treatment be ECT. Nash's wife and colleagues refused that "brain-damaging treatment" and he was continued on medication with chlorpromazine. Nash did not recover and did not return to productive work; he remained cared for by his wife and attended lectures at Princeton.

Nasar's biography *A Beautiful Mind* was to be the basis of a Hollywood film and she wanted advice on the actual experience of the treatments that Nash had been given.[47] I described my experience at Hillside Hospital, noted that seizures occurred in more than 10% of the coma sessions. The film highlighted the seizure, and I was pleased by the portrayal of the illness and the treatment in the film.[48]

I was stimulated to review my experience with insulin coma and concluded again that the central therapeutic events were the incidental seizures, not the coma or an effect of insulin, or any other aspect of the treatment.[49] Like injections with camphor and Metrazol, insulin coma was best viewed as an inefficient form of induced seizure therapy. As the originator of ICT, Manfred Sakel insisted that the comas selectively destroyed sick brain cells leaving only healthy cells.[50] He argued that the seizures were incidental, irrelevant side-effects. But experienced clinicians welcomed the seizures and often added ECT during coma sessions for the poorly responsive.[51]

The Sackeim Regressions

Harold Sackeim, the clinical psychologist discussed briefly in earlier chapters, has had an obsessive interest in the effects of seizures on cognition and memory. He has profoundly influenced the practice and history of ECT, more so than any other person in the past 40 years.

A fellowship at Oxford University in 1974 sparked his interest in human memory. After obtaining a doctorate in psychology at University of Pennsylvania, he joined the faculty at the New York State Psychiatric Institute as a research psychologist, focused this interest on the effects of ECT on memory, and soon received funding from NIMH and other agencies for a study of cognition in ECT. After measuring the immediate cognitive changes induced by seizures, and confirming the lesser impact of unilateral electrode placements, he focused on further reducing the impact on memory by modifying the energy levels and currents used to induce seizures. Beginning in early 1990s he designed a seizure threshold measure (ST), using minimal currents repeatedly in the first treatment until a seizure was elicited.[52] Reluctantly accepting the induction of a seizure as necessary, he examined RUL treatments at doses of 1.5x and 2.5x the calibrated seizure threshold, expecting successful clinical benefits on the assumption that all seizures were equally effective, finding that the clinical efficacy was severely reduced. His enthusiastic presentations at meetings encouraged others to follow his lead, until it became clear that ST dosing required a minimum of 6x ST to achieve minimal clinical benefit with RUL ECT.[53] At these levels the efficacy still does not approach that of bilateral treatments using age-estimated dosing practices nor does it minimize the effects on cognition. Sackeim, it should be said, is not a physician and bears no responsibilty for the clinical care of the experimental subjects in these experiments.

Seeking other methods of reducing effects on memory, Sackeim next enthusiastically recommended non-seizure brain stimulation by Transcranial Magnetic Stimulation (TMS), then by Vagus Nerve Stimulation (VNS), stimulating limited brain areas by focal magnetic currents (FEAST), and eliciting seizures by magnetic currents (Magnetic Seizure Therapy, or MST). Not one of these variations enhanced treatment efficacy, but he claimed benefits of reducing the effects on immediate memory tests. A more recent effort has been to convince device manufacturers to modify the pulse width of the electric currents to “ultra-brief” forms. These currents are also less efficient and reduce treatment efficacy.

The weakness of his electric current and electrode manipulations is demonstrated in the comparison of the parallel NIMH-supported collaborative ECT studies discussed in the preceding chapter as the Columbia Consortium (CUC) and the CORE consortium. Both used the same criteria for inclusion of patients in the study and the same outcome criteria. The singular distinction was in the electrode placements -- CUC patients were treated using right unilateral

electrode placements, the CORE patients by bitemporal electrode placements. The clinical efficacy outcomes of CUC patients was 54% with a mean of 10 treatments, that of CORE patients was 84% and a mean of 7 treatments.[54] Many of the CUC patients required added bilateral treatments for a successful outcome. Despite his claims, the cognitive effects of the two treatments were indistinguishable immediately after treatment and at reexamination at various times after the treatment course.[55]

The influence of Sackeim on the profession has been profound. He is easily recognized world-wide as the principal ECT authority. His teaching encourages treatments to be done poorly with lower rates of recovery, higher relapse rates, prolonged treatment courses, and increased treatment failures. Lengthened courses of continuation treatments are now common, especially for patients treated with the modified unilateral electrode placements and ultra-brief square-wave currents that he has espoused. Inefficacy is guaranted by the use of the seizure threshold estimation for treatment parameters.[56]

Despite the recurring reports of lesser efficacy of these manipulations of energy currents, Sackeim's strident voice at professional and public forums, ostensibly supporting the treatment but warning of persistent, even permanent, memory loss, and his witnessing against practitioners in the courts has dominated the practice of ECT world-wide.[57]

When Sackeim began his studies I supported his efforts. I was a member of the review panel that approved his CUC Consortium study and I did vote to approve the application. I invited him to join the Editorial Board of *Convulsive Therapy*, and recommended he edit a special number dedicated to "Mechanisms of Action."[58] In 1994, when I considered stepping down as the journal's editor, I invited him to be considered as my replacement, but he demurred.

Neurostimulation – A False Alternative.

In the 1980s, devices that deliver pulsed magnetic currents were developed to stimulate peripheral nerves and the brain. Few reliable clinical applications were found but manufacturers searching for some clinical use and a financial return recognized the image similarity to ECT and paid clinicians to apply the currents to treat depression. The first experiments in neurology patients found little benefit, but when the method was applied in long-term depressed patients who met criteria for psychoneurosis or hysteria (the worried well) and who had previously failed to get relief from medications, some were temporarily relieved by the scalp stimulating sessions.

While the effects were modest, TMS devices were marketed as replacements for ECT. Direct comparisons with ECT, however, showed these TMS episodes to be ineffective compared to induced seizures in seriously ill patients.[5960]

Delivering very high magnetic energies to the skull of humans and other animals may elicit a seizure, a procedure labeled magnetic seizure therapy (MST). This technique was also offered as a replacement for ECT. As of this writing (January 2017), seizure inductions using this method are unpredictable, the experience limited to laboratory settings, and no proper studies have reported clinical efficacy. The MST enthusiasts argue that effective seizures can be elicited with lesser effects on memory performance and tests. Like unilateral electrode placement and ultrabrief currents, this seizure induction method will fail. The devices are complex and expensive, and the efficacy is too poor to replace electrically induced seizures.

Other methods of "neurostimulation," labeled deep brain stimulation (DBS), vagus nerve stimulation (VNS), and transcranial direct current stimulation (tDCS), are touted by well-financed commercial device manufacturers that are at the core of the neurostimulation movement. Each is promoted as an alternative treatment to ECT. As I watched the developing enthusiasm alter both the aims of the *Journal of ECT* and the mission and presentations of the Association for Convulsive Therapy, I protested publicly arguing that none of these methods are alternatives for induced seizures and refused to join the society.[61]

06: The Enigma of How Seizures Alter Behavior

Grand mal seizures are patterned reflexes that are seen in our species, indeed in all mammals. Seizures that occur spontaneously constitute the debilitating disease of epilepsy. Ladislas Meduna's 1934 discovery that inducing seizures in the psychiatric ill relieved abnormal thoughts and the peculiar and repetitive motor behaviors of schizophrenia was a remarkable and still unheralded discovery in the history of medicine. By 1938 electric currents had been shown to immediately induce a seizure with minimal pain and less risk than Meduna's chemical method, and the electrical induction of seizures -- electroshock -- quickly became a widely accepted treatment of the severe psychiatric ill.

The induction of a bilateral grand mal brain seizure is the central therapeutic event. A patterned EEG of a minimum duration of 30-40 seconds is the principal marker of an adequate treatment. An increase in hypothalamic-pituitary hormones in the blood and cerebrospinal fluid is another marker. No characteristic of the induction stimulus itself, whether chemical or electrical, is essential for clinical benefits, as we've seen. Attempts to treat patients by subconvulsive electric or magnetic currents or by non-seizure inducing chemical dosing have been unsuccessful in eliciting behavioral benefits.[1]

Although many patients report immediate changes in mood, motor activity, and thought, repeated seizures over many days or weeks are typically necessary for lasting clinical benefits. Attempts to sustain the clinical benefits by psychotropic drugs are occasionally successful, but for persistent benefits repeated seizures are best.

How do seizures alter behaviors? We do not know. My thinking on this question has evolved over the years. Early in my career and with the hubris of the novice I combined physiological and psychological features in "a unified theory of the action of physiodynamic theories."[2] That construct was re-labeled the *neurophysiologic-adaptive* view a few years later.[3] I argued that the changes in behavior, toward greater denial of illness, was facilitated by altered brain physiology.

My studies with anticholinergic compounds showed me that drugs that inhibit brain acetylcholine reversed the mood benefits of ECT. The elevated levels of brain acetylcholine associated with recovery in mood and thought seemed sufficient to justify what in 1962 I described as a *cholinergictheory*.[4] I argued that seizures increased the brain levels of acetylcholine and the cholinesterases, and that these changes altered neuroendocrine functions,

mainly of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes. This hypothesis was consistent with the ongoing enthusiasm for changes in the brain humors that were thought the basis for the changes in behavior associated with psychotropic drugs.

As chemist's skills improved and concentrations of endocrine hormones in the blood could be measured, my interest focused on vegetative signs in psychiatric illnesses. Attention to the TSH hormone response to TRH and abnormal thyroid physiology was quickly followed by interest in adrenal hormones and the dexamethasone suppression test in depressive illness. Not only were thyroid and cortisol abnormalities markers in the psychiatric ill, the abnormalities normalized with effective treatments.[5] I sought to confirm these reports in our patients treated with ECT at the Northport Veterans Administration hospital in Eastern Long Island.[6] When Jan-Otto Ottosson also saw merit in a neuroendocrine image of ECT, we formulated a *neuroendocrine theory* that we published in 1980.[78] At this writing I believe this theory remains the most viable explanation for the efficacy of induced seizures in patients ill with melancholia. While this theory may not be applicable to the benefits in other psychiatric illnesses, it is a pointer that warrants greater study.

The Theories

The magic of the changes induced in the psychiatric ill by the bizarre technology of repeatedly inducing grand mal seizures is puzzling and has encouraged a plethora of theories, some based on brain and body physiology and chemistry, and some on magical thinking. My ruminations and their origins have evolved with my experience.

Neurophysiologic-adaptive theory. At Bellevue Hospital in the 1940s my teachers were much interested in anosognosia, the failure of awareness or the active denial of a deficit in motor functions (as in post-stroke) or denial of sensory loss (as in denial of blindness[9]), as I described in Chapter 1. Special attention was paid to how humans perceived multiple stimulations as when two pinpricks or finger strokes were simultaneously applied to different body parts.

Even in patients with brain functions compromised by trauma, age, infection or tumor, a single sensory stimulus is readily perceived but the perception of two simultaneous stimuli varies with the subject's alertness and vigilance. The errors were evidence of compromised brain functions, of the syndrome loosely described as the "organic mental syndrome." After head injury, stroke, brain tumor, aging, infection or repeated seizures, only one stimulus is reported

(extinction), or the second stimulus is perceived at another body site (displacement), or pointed into space before them (exosomesthesia). Under the influence of injected amobarbital, perception errors and the expression of denial language increase. These reports became the basis for the *Face-Hand Test*.[10]

During the course of treatment, errors increased with numbers of treatments. The greater the degree of EEG change, the greater the perceptual errors.[11] Among the scientists at Bellevue, Edwin Weinstein, Louis Linn, and Robert Kahn proposed "denial" as the mechanism for the relief afforded depressed patients by electroshock.[12] They catalogued a "language of denial" making it possible to score the number of denial terms in an interview transcript. When amobarbital was injected at a fixed concentration and a specified rate, the number of expressed denial terms increased, especially in brain compromised patients.[13]

I studied the expression of denial during ECT by weekly amobarbital and EEG tests and recording patient responses.[14] As EEG slow wave activity increased with more seizures, so did expressions of denial in those patients who showed the greatest relief of depressed mood.[15, 16] I adopted this explanation of the changes in behavior during ECT as an increase in denial. Depressed patients commonly complained of insomnia, anorexia, fatigue, weakness, and loss of interest in their daily activities. After treatment, the complaints were relieved and when asked what was wrong, they denied their earlier complaints. Since the connection between denial and improvement had been proposed by my teachers, and as EEG and sedation tests verified their proposition, I adopted denial as an explanation. I did not seek greater understanding of physiology until years later.

Such an explanation was applicable in the patients with melancholic and psychotic depression, but was not relevant for the response of those in delirious states, catatonia, mania, or psychosis. These states are marked by disorientation and confusion, mutism and negatism, hyperactivity and disorders in thought that needed broader explanations than the simplistic denial of symptoms. Their responses required another explanation.

Cholinergic theory. My interest in the effects of psychoactive drugs on the EEG led me to study the effect of drugs on the ECT process. A colleague, Herman Denber, interested me in studying the behavioral effects of diethazine, an experimental anticholinergic drug that had its action in blocking acetylcholine stimulation. The chemical was a new moiety created in industry with the hope that it might have clinically favorable psychoactive properties that he was testing.

He was unable to identify a clinical benefit, finding that patients became more disorganized and irritable with its administration. I administered diethazine to our improving ECT patients, those with signs of denial and recovery from a depressive state and with high degrees of EEG slowing. The slow waves were blocked and the records became filled with low voltage fast rhythms.[17] Patients became irritable, anxious, agitated and again depressed, a reversion to their pre-treatment states. We inferred that the relief of depressed mood with ECT was related to increased levels of acetylcholine in the brain.

George Ulett and his colleagues at Washington University had administered atropine, a potent anticholinergic drug, during the ECT treatment course and reported that it blocked EEG slow waves and elicited pre-treatment behaviors in the patients.[18] Similar reversal of mood was also reported after injections of the experimental anticholinergic drug JB-329 (Ditran) and its congeners, supporting the connection between brain cholinergic levels and mood. [19]

Much interest was shown in acetylcholine in neuroscience research in the 1950s. Free acetylcholine and acetylcholinesterases were elevated in the cerebrospinal fluid (CSF) of epileptic patients.[20] CSF acetylcholine levels increased during ECT.[21] In cats subjected to graduated head trauma, the amount of free acetylcholine and cholinesterases in the CSF increased with the severity of the trauma.[22] Again, my hubris allowed me to picture the physiologic consequences of induced seizures as similar to those of head trauma.[23]

I imagined that induced seizures, like cerebral trauma and epileptic seizures, altered cerebral permeability to increase free acetylcholine and cholinesterases in the brain, slowing EEG frequencies and increasing amplitudes and rhythmic bursts. I pictured these biochemical changes as the basis for the behavioral effects we were seeing with ECT.[24]

My focus on acetylcholine as the critical agent in treatment followed the happenstance finding that anticholinergic agents reversed the seizure-induced EEG and behavioral changes. But study interest in acetylcholine waned as interest in brain neurotransmitters shifted to epinephrine, and then to dopamine and serotonin, as pharmacologists, excited by their ability to measure these neurotransmitters in animal brains tracked the effects of each of the new psychoactive moieties, which were enthusiastically welcomed by clinicians and the public. At this juncture, half a century later, I find little interest in acetylcholine in clinical psychiatry or epilepsy. The cholinergic hypothesis remains intriguing, nevertheless, with a frustrating set of observations that relate brain chemistry, illness behaviors, and the response to induced seizures.

The question is one of many ignored by neuroscientists who have no interest in the unique benefits observable by inducing seizures as treatments.

ANeuroendocrine Hypothesis. When I was asked in 1977 to supervise an acute treatment unit and its ECT facility at the Veterans Administration hospital in Northport, much academic interest was being shown in brain peptide hormones in the psychiatric ill, particularly those of the thyroid, adrenal and pituitary glands. The Nobel Prize for Medicine that year was awarded for the demonstration of peptide hormones in the brain and for the radioimmune assay that measured their presence.[25]

Hormone changes in our patients became measurable by thyroid and adrenal function tests. These glands are instrumental in maintaining the daily wakefulness cycle, the response to fear and stress, and monitoring sleep and other bodily functions. The TRH stimulation test, the release of TSH to an intravenous bolus of TRH, was blunted in a quarter of the severely depressed patients.[26] After a course of ECT, we did not find the changes in TRH levels that we had hoped would help us decide whether the treatment course was successful, and whether additional treatments would be helpful.[27]

Cortisol derived from the adrenal gland was a more useful marker. Serum cortisol levels were unusually elevated in institutionalized depressed patients, an observation in the 1970s that led an Australian psychiatric team under Brian Davies and Bernard Carroll to study cortisol functions in their patients. They developed the dexamethasone suppression test (DST) as a measure of adrenal function.[28] Their reports are filled with extensive observations of hormone functions and psychiatric illness but the note that particularly stimulated my interest was their experience with ECT in melancholia.[29]

In five melancholic patients the cortisol measures were deemed abnormal (elevated and not suppressed by the steroid dexamethasone) before treatment. After ECT the clinical features of melancholia remitted and the cortisol measures normalized. Then two of the patients relapsed, again exhibiting signs of melancholia with abnormal cortisol functions. Second courses of ECT resolved the clinical illness, again normalizing the cortisol measures. Carroll described an additional seven patients in whom treatments had not resolved the depressive illness nor normalized the DST. The test, it seemed, was a marker of illness severity and of treatment response.

At the Northport hospital a research fellow Yiannis Papakostas[30] confirmed the relationship between severity of depression, abnormal DST, and the response to ECT that Carroll had described.[31] The test was difficult to perform and the end-point criteria needed more careful study, but the changes in the neuroendocrine tests with improvement in melancholia led to more detailed studies of the response to ECT.

Seizures, both in epileptic fits and in those induced in ECT, released the pituitary adrenocorticotrophic hormones (ACTH) and prolactin in the CSF and blood. By 1978 attention was directed to the association of the contributions to behavior of the products of the hypothalamus, pituitary and adrenal glands, (HPA axis) in melancholic depression and the response to ECT. At the 1978 New Orleans NIMH Conference on ECT, I described my experience with the DST, supporting Bernard Carroll's experience. At the same conference Jan-Otto Ottosson independently supported the endocrine findings. Melancholic psychotic patients have abnormalities in functions of the HPA endocrines, and these return to normal after recovery.

I described a "neuroendocrine" hypothesis for ECT[32] in *Convulsive Therapy: Theory and Practice* and cited what was known of the process:

> "*A theory of convulsive therapy must account for the significance of the seizure but disregard the mode of induction, the direct actions of currents, and the distinctions caused by various electrode placements. It must consider the difference in response among patients with diverse psychopathologies and the time, measured in days, needed for a favorable outcome. Biochemical explanations must relate to changes in the brain rather than in the blood, urine or other tissues. Psychological, personality, and linguistic considerations may affect the behavioral response and should be considered, but these are probably not central to the antidepressant efficacy of induced convulsions*."

And I described the hypothesis thus:

> "*Hypothalamic dysfunction is a core process in endogenous depressive psychosis. Convulsive therapy alters hypothalamic activity both by direct stimulation of hypothalamic cells and by increasing the functional neurotransmitter activity in the brain, thereby releasing substances, probably peptide hormones, that alter the vegetative functions of the body and the endocrine glands. Specific substances are released that modify mood and the behaviors associated with mood disturbances. The biochemical*

> *events that precede and accompany the seizure are the trigger for increased neurohumoral activity. In ECT, the direct stimulation of electric currents augment but are not necessary for the effects on hypothalamic functions*."

The mechanism was envisioned for patients with psychotic depression in whom the efficacy of ECT was well grounded, inducing remission in more than 90% of the cases. In the same chapter I discussed the evidence for ECT's effect on mania, catatonia, and schizophrenia. While the treatments were successful in mania and catatonia, we lacked studies of endocrine changes to support a connection similar to that with melancholia. In schizophrenia the efficacy of ECT was insecure, being successful in acute illnesses and in catatonia, but ineffective in the more common chronic ill with the hebephrenic and other forms of the illness. [33]

In the 1980s I attempted a study of peptides in the cerebrospinal fluid during ECT to develop my hypothesis. Of nine patients with psychotic depression referred for ECT with mean scores on the Hamilton Depression Rating Scale greater than 25, eight were non-suppressors on the DST. I collected their lumbar CSF before ECT and then after treatments number 6, 10, 12 and 14. The samples were collected within one day after a treatment, and in five patients additional treatments were deemed necessary. The frozen samples were shipped to Charles Nemeroff and Garth Bissette at Duke University and to Huda Akil at the University of Michigan for analyses for the peptides of the corticotrophin-releasing factor, somatostatin, and beta-endorphin. The samples showed significant falls in levels of corticotrophin releasing factor and β-endorphin but a non-significant rise in somatostatin.[34]

The findings were not encouraging to the neuroendocrine hypothesis. While the hypothesis could be erroneous, our actual procedures did not meet the more optimal criteria that would be used today. We made arbitrary choices in our treatment mode. We used unilateral electrode placement with EEG monitoring of seizure duration, selected sampling in mid-course of treatment, with varying resolution of the illness and the DST, and were only able to test for a limited number of peptides. The study demonstrated the complexity of studies of the ECT mechanism. While I was interested in proceeding further, I lacked facilities for chemistry. Instead, I was in a position to pay more attention to the clinical questions of the ECT process that became the CORE studies undertaken between 1993 and 2005.

Searching for an Explanation

Believing that it must be possible to understand the relief of certain psychiatric illnesses by inducing seizures, I have participated and encouraged discussions of possible mechanisms throughout my working life. Surely the extensive experience that inducing seizures improves the behaviors and the lives of many severe mentally ill must be a challenge in present day biology. What follows is a chronological account of moments in this endeavor.

1972. The first encouragement in my interest came in convincing a committee at the NIMH to support a symposium on ECT mechanism. The committee asked two leading neurobiologists, Seymour Kety and James McGaugh, to join me in organizing a 1972 meeting in San Juan, Puerto Rico, titled *Psychobiology of Convulsive Therapy*.[35] Attention was focused at the meeting on the neurophysiology of seizures, the role of changes in cognition, and the neurochemistry of catecholamines.

The panelists concluded that persistent changes in EEG recordings were deemed essential to the behavior changes in the therapy. In the absence of persistent EEG changes, only weak and transient behavior effects occurred.

Changes in memory were not essential to the behavior benefits. The complaints of loss of recent memories were side-effects of the electricity, the anesthetics, and the seizure. The changes were not central to the effects of seizures on mood and thought.

Much interest was shown in the actions of newly discovered brain neurotransmitters that "explained" the effects of psychoactive drugs on brain functions and behavior. Changes in the neurotransmitters were considered an explanation of the behavioral effects of repeated induced seizures as well. Seymour Kety cautioned, however, that

> *". . . there is no dearth of demonstrable biochemical changes which are associated with electroconvulsive shock. Indeed, the difficulty lies not in demonstrating such changes, but in differentiating between those which are more fundamental and those that are clearly secondary, and also in attempting to discern which of the changes may be related to the important antidepressive or amnestic effects and which are quite irrelevant to these.*"[36]

In the 45 years since that meeting, the ECT literature has been filled with correlations of brain and systemic increases of many biochemical and behavior measures.[37] But no study has offered

a consistent association between neurotransmitter functions and changes in mood and thought, either for induced seizures or for the many psychoactive pills.[38]

1978. Continuing interest in ECT encouraged NIMH leaders to organize a larger conference in February 1978 in New Orleans on "Efficacy and Impact" with a larger panel of clinicians and scientists.[39] In the six years since the San Juan Conference interests had broadened to the safety of regressive ECT (intensive daily treatments that were applied in chronic psychotic patients), the efficacy of different electrode placements, changes in electric currents from alternating to brief pulse currents, the clinical usefulness in patients with mania and schizophrenia, and the relation to endocrine measures. At this conference I became aware that Jan-Otto Ottosson had also been stimulated to examine the changes in neuroendocrine measures, and we joined in publishing the neuroendocrine hypothesis for the mechanism of induced seizures in *Psychiatry Research* in 1980.[40] I was so impressed with the relation of neuroendocrine changes to behavior that in writing my 1979 textbook *Convulsive Therapy: Theory and Practice,* I credited the neuroendocrine explanation for ECT as the most viable.[41]

1985. The hostility toward and controversy about ECT encouraged the NIMH to hold a public Consensus Conference in October 1985.[42] Although the panelists included experienced practitioners, greater attention was paid to the critical opinions and biases of lay and professional critics. The discussions were raucous and were accompanied by shouting and hostility. The published reviews added little to either the clinical or the mechanism interests, reflecting the continuing rejection of and prejudice against the treatment in the public and the professions.

1986. Motivated by the circus of the Consensus Conference, Sidney Malitz and Harold Sackeim organized a conference at the New York Academy of Sciences in 1986. The presentations covered the broad issues of clinical efficacy varying with diagnosis, results of biochemical, neurophysiologic, neuroendocrinologic, and psychologic changes during the course of treatments, and mechanisms of action. Jan-Otto Ottosson detailed the essential characteristics of an effective seizure and treatment course; Bernard Lerer and Baruch Shapira looked at the impact of seizures on neurotransmitters; and Robert Post and his NIH colleagues discussed the anticonvulsant effects of seizures. They saw the anticonvulsant effects in mania in the therapeutic stream, endorsing anticonvulsant medicines to treat manic behaviors. Harold Sackeim and colleagues reported a rise in seizure thresholds during the course of ECT treatments, arguing that the benefits of induced seizures were in the anticonvulsant

effects.[43]Pierre Flor-Henry focused attention on the theoretic lateralized changes in the non-dominant hemisphere as the basis for the behavior change with seizures. These proposed mechanisms were no more exciting than the presentations a decade earlier in the San Juan conference, and they stimulated little further study.

1989. Still hoping that invited discussions might encourage study, and as Editor of the journal *Convulsive Therapy*, I asked Harold Sackeim to invite authors with an interest in the mechanism to write reviews for a special number of volume 5.[44]An impediment to formulating a single hypothesis is the efficacy of induced seizures across the broad spectrum of psychiatric disorders. Surely, no single mechanism can explain the diverse effects in melancholia, mania, catatonia, delirium, and Parkinsonism.[45] The same hurdles were described by Pesach Lichtenberg and Bernard Lerer[46] and by Sukdeb Mukherjee in discussing the relief of mania.[47] In a reprise of the debates on the merits of unilateral electrode placements, Richard Abrams challenged the reported advantage for treatments induced in the right hemisphere rather than the left, raising the importance of the details in any induced seizure study seeking to understand mechanism.[48] Charles Nemeroff and I, in the midst of our collaborative studies of peptides in CSF, asked whether we anticipated higher or lower levels of peptides as the basis for melancholic depression and relief by ECT.[49] We favored the image of lower levels of peptides active in maintaining normal mood and suggested that the seizures might release an active peptide that we named *antidepressin*. Our optimism in picturing an additional peptide was generated by the increasing number of substances that were being publicly characterized as altering mood, alertness, and cognition in the psychiatric ill. But, nothing has come of it, another nagging consequence of my not having developed skills in biochemistry.

1992. In editing a second edition of his textbook Abrams repeated the diversity argument that the efficacy of induced seizures over many illnesses made theorizing not particularly useful until a better understanding of psychiatric illness emerged.[50] He saw our understanding as similar to that of the peoples in the 18th Century picturing burning as a process involving the imaginary substance phlogiston. He concluded that we await the intervention of a modern Anton Lavoisier, the French scientist who discovered oxygen, 20% of the air we breathe and the basis for burning substances by their combination.

1998. The continuing challenge of mechanism led Charles Kellner, the succeeding editor of *Convulsive Therapy*, to ask Bernard Lerer to invite opinions on what was learned about the

neurobiology of seizures. Lerer again complained of the difficulty of seeking a single mechanism for a procedure with such a broad effect among many disorders.[51] Reviews by John Mann[52] and Ron Duman[53] were no more useful. Nor was an explanation based on the anticonvulsant actions of seizures.[54] Studies of the brain neurotrophic factor, neuropeptides, TRH and related peptides, and neuropeptide Y each fell to the criticism by Kety that the broad effects of seizures on many brain chemicals made it unlikely that changes in any single measure would be relevant to the mechanism. At best, any single measure would be a marker of the breadth of the changes induced in brain biology.

2014. Recently I encouraged Vaughn McCall, the present editor of the *Journal of ECT*, to organize another review of mechanisms. He asked Pascal Sienaert[55] to organize the reports that were published in June 2014.[56] Each survey considered the main measurable consequences of seizures – changes in the EEG and psychological tests, neurotransmitters, neuroendocrines, and immune and cardiovascular systems. I chose to remind readers that the central event was the seizure and not in any aspect of electricity, by noting the equivalent efficacy and consequences of flurothyl induced seizures to those induced electrically.[57]

Roger Haskett of the University of Pittsburgh discussed the neuroendocrine hypothesis.[58] Haskett had studied cortisol in melancholia and ECT in collaboration with Bernard Carroll when both were at the University of Michigan in the 1980s. In his review Haskett supported the endocrine hypothesis as well documented but bemoaned the overall lack of interest in endocrine studies in psychiatry.

In retrospect, the discovery of the changes in human behavior by repeated inductions of seizures is a remarkable page in the history of medicine. As I read the invited articles on mechanism submitted to *JECT* in 2014, I do not see a better explanation than that of the impact of seizures on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid systems and regret that I did not dedicate more energy or had the skill to understand this powerful mechanism.

07 The New Science of Clinical Psychopharmacology

My training in medical school and residencies offered little experience with medicines for the psychiatric ill. Excited and aggressive patients were physically restrained by linen jackets and leather straps, in isolation rooms, and sedated in prolonged sleep with bromides, barbiturates, and opioids. The mute, negativistic, and stuporous catatonic patients were treated with barbiturates, an effective treatment well known since 1930. Electroshock, insulin coma, and lobotomy were widely used to treat the more severely agitated, depressed, and psychotic patients.

The introduction of chlorpromazine to Hillside Hospital in the autumn of 1954 quickly excited much interest with its promise of controlling psychosis and aggressivity without stupor, the usual experience with prior medicines. Nurses who saw its first use were impressed by the rapid reduction in excitement and recommended their patients for treatment trials when it was introduced as an experimental treatment. Some nurses asked for its use instead of insulin coma, encouraging me to undertake the random controlled trial comparing chlorpromazine with insulin coma.[1]

At this beginning of the psychopharmacology era I was in a favorable position to study the new agents while supervising the electroshock and insulin coma units at Hillside. Individual and group psychoanalytic and milieu therapies were the flagship treatments offered patients who were admitted for voluntary in-hospital stays for as long as a year. A decision to refer a patient for ECT or ICT represented, in the eyes of the residents and teachers, a failure of their psychotherapy skills and "resistance" to understanding by the patients. The clinicians lost interest in the patients that couldn't be helped by their favored psychodynamic methods.

In this research environment, we who were responsible for ECT and ICT were also in a position to prescribe the new experimental medicines as each became available for study. We soon asked, for whom was each agent useful? Which behaviors were relieved? What were the effective doses? How were the medicines identified and classified?

As we were recording the EEG in our ECT patients, we could easily record the effects of each of our psychoactive drugs, first with amobarbital, reserpine and LSD, and then chlorpromazine and imipramine, and as these were classified, to identify patterns for each newer agent. We observed different patterns of change in EEG frequencies for the different chemicals and as we related the ECT induced changes to behavior, we sought similar relationships for the

new agents.

Chlorpromazine, imipramine, and each new agent influenced different behaviors and different EEG profiles. Chlorpromazine muted aggressive, overactive, and strange thoughts, increasing the slower EEG frequencies and amplitudes, decreasing the fast frequencies. As doses rose, occasional seizure bursts were recorded. With imipramine, patients became more alert and active, slept and ate better, and ruminated less. Both slow and fast EEG frequencies increased. With chlordiazepoxide, agitation and excitement diminished, sedation and sleep increased accompanied by increases in EEG fast frequencies with well-modulated runs of waves described as "spindles."

Did the EEG pattern predict a drug's effects on behavior? The EEG patterns reflected the agent's impacts on brain chemistry. Psychoactive agents that altered human behaviors did so by altering brain chemistry, measurable in the EEG record. Though the patterns varied with each agent, we soon clustered agents by the similarity of their EEG profiles. We had begun with hand measurements of height and width of each EEG wave during the course of ECT, but replaced this method by measurements using an electronic frequency analyzer at Hillside in 1959, and then, after I had moved to St Louis, by digital computer methods based on IBM equipment. In the next decades, we established that each new clinically active agent altered the human EEG in systematic ways, establishing a science of pharmaco-EEG.[2] (These are described in Chapter 9.)

The classification of mental illnesses at the time was based on criteria described by the European deans of psychopathology Emil Kraepelin, Eugen Bleuler, and Adolf Meyer. The first official classification of mental disorders endorsed by the American Psychiatric Association, the Diagnostic Statistical Manual (DSM-I) was published in 1952. It identified each disorder that the editors thought that they could recognize. The labels were imprecise, unverifiable, and their use varied with time and with the training and experience of the observers. No test to verify any diagnosis was available; each label was akin to bird watching and identification, subject to the experience and knowledge of the observer. When applied to patients, the labels helped little in the choice of treatments or prognosis. For more precise descriptions we scored rating scales that listed each sign of behavior that could be qualified by severity and described the effects of treatment by studying changes in the symptoms and symptom profiles. We soon identified pharmacologic agents that altered prominent behaviors and pigeonholed the effects as antipsychotic, antidepressant, and anxiolytic. The terminology became the *lingua franca* of

psychopharmacology writings.

Our thinking at Hillside was strongly influenced by the psychodynamic culture of the hospital and the psychiatric community. If we could not identify diseases, perhaps we could identify character and personality traits that energized the behaviors and use changes in those behaviors to measure symptom improvement. Tests for intelligence, such as the Wechsler Bellevue and the Stanford Binet tests, were administered to all patients on admission to measure their understanding of language and to estimate their facility to participate in psychotherapy. Character was measured by the responses to the Rorschach inkblot test, California F Scale, and the Bender Gestalt tests. We hoped that patient responses to these tests before treatment would offer guides to the prescription of the medicines and retesting after treatment would give us quantitative measures of changes associated with medication use.

How were the new medicines initially selected for the clinic? We lacked systematic ways to identify the likely effects in our patients. Much interest was focused on the neurotransmitters acetylcholine, epinephrine, and norepinephrine; later, interest shifted to dopamine, serotonin, and gamma-aminobutyric acid (GABA). Changes in brain neurotransmitter levels and their receptors in various animals became markers of drug effects used by industry and academic researchers to select compounds for clinical trial and to predict the populations in which the chemicals might be beneficial. When I studied the EEG profiles of the agents and compared the observations in human beings to those recorded in other animal species, I realized that the predictions from animal trials were poorly related to those in humans because of species specificity in metabolism, preferred foods, day-night cycles, and the absence of behavior dysfunctions that could be related to those in humans. Yes, human research was difficult, expensive, and limited by ethical concerns. Animal trials were all that both industry and academia had available.[3]

Unfolding Pharmacology Experience

Our first psychopharmacology studies were of the influence of amobarbital on denial language and on the perception of simultaneous stimuli. Reserpine was the first new psychoactive agent we studied, followed by the hallucinogen LSD-25.

Amobarbital. Barbiturates sedated the unruly, induced sleep, and relieved anxiety. Its high therapeutic index (separation of the effective, safe dose from the dose that would be toxic) and their widespread use during World War II was reassuring as to its safety. Edwin Weinstein

and Robert Kahn, as we've seen, showed that denial language increased after administration of amobarbital, and its administration was a useful measure of brain functions.[4] They also applied their experience with amobarbital to a theory of the mode of action of ECT.[5]

During the course of ECT, errors in orientation, increased denial language, and increased errors in the Face-Hand test are accompanied by slowing of EEG frequencies.[6] The changes reflect the enhancement of what was termed at the time an "organic mental syndrome"--alterations in orientation, awareness, cognition that are secondary to trauma, stroke, tumor, or infection.

Another test use of amobarbital, described by Charles Shagass,[7] reported that the dose of amobarbital needed to elicit EEG beta spindling, a recognizable EEG pattern, varied with the severity of the patient's anxiety. The greater the anxiety, the higher the amobarbital dose needed to elicit EEG spindling. The number of milliliters of amobarbital intravenously administered at the rate of 1 mg every 40 seconds needed to elicit EEG spindling was defined as the "sedation threshold."[8] We confirmed his observation. We also reported that nystagmus (repetitive eye gaze movements on lateral gaze) occurred at the same time as beta spindling and suggested that the sedation threshold could be measured by visual observation alone, without the EEG.[9]

Assured of the safety of amobarbital injections, I used such tests freely in my clinical practice. Later in my career, when I developed an interest in catatonia, I supported the relief of mutism, negativism and posturing by amobarbital, an application that was soon replaced by lorazepam and diazepam as verification of the catatonia diagnosis and as treatments.[10]

Reserpine. A *New York Times* front page story titled *Indian Drugs for Mental Diseases* on May 31, 1953 aroused great interest. R. A. Hakim, a western-trained Indian psychiatrist reported greater clinical benefits with convulsive treatments when the native Ayurvedic medicine *rauwolfia serpentina* (reserpine) was added during the treatment course. Was reserpine itself psychoactive? At the time, we were treating an 18-year old psychotic and agitated woman who had not responded to either insulin coma or electroshock treatments. When her father, an international sales representative, asked about alternative treatments for his daughter, I offered to treat her with reserpine if we could obtain a supply. A few weeks later he delivered a box with 25 ampules of 5 mg reserpine each from the Ciba firm in Switzerland. We administered increasing doses to his daughter and to selected other patients, but found little benefit and

considerable difficulty with motor rigidity, slowness of movement, and posturing. We referred her for other treatments.

Regular dosing with reserpine lowered systolic blood pressures accompanied by decreases in expressed fears and anxieties. We developed a 12-week study of daily dosing with either 5mg or 10 mg reserpine or placebo in a random controlled trial of patients with severe anxiety and agitation. Reserpine-treated patients became sedated, less agitated, and less anxious. Four, however, became so depressed as to require treatment with ECT, heralding the later recognized risk that reserpine treatment worsened depressive illness.[11] Our interest in reserpine waned.

Chlorpromazine. Largactil had been developed in France as a sedative, reducing excitement and psychosis of the psychiatric ill. Henry Brill, the Medical Director at Pilgrim State Hospital, had asked research directors at various New York State hospitals to test the medicine. At an open meeting organized at Creedmoor State Hospital in Queens in 1954, I heard one researcher after another -- Herman Denber, Nathan S. Kline, Sidney Malitz, Sidney Merlis, Anthony Sainz, and John Whittier -- report reduced excitement, aggression, and mania, lesser disorders in thought, fewer injuries to patients and staff members, fewer fires set, fewer mattresses trashed, and fewer windows broken with chlorpromazine use. At the end of the sessions representatives of the Smith, Kline and French pharmaceutical company offered 25mg samples for clinical trials and I enrolled.

As the dosing and risks of chlorpromazine were poorly known, the Hillside hospital administration decided that referrals for this experimental treatment were best prescribed only by the ECT/ICT physicians. For the first trials we selected the most disturbed and least cooperative patients in one study unit. Soon after beginning the medication, patients became more responsive, less aggressive and manic, and more cooperative. Soon, nurses from other units asked whether we would enroll their patients. Initially reluctant staff attitudes changed quickly and our enthusiasm for chlorpromazine was added to the international voices encouraging its use from France and Canada.

But soon one patient, and then another developed jaundice. Other centers reported similar toxicities. Our patients were examined for systemic liver disease, but no explanation for the jaundice was found. Our initial enthusiasm for chlorpromazine trials became inhibited, but the strength of the benefits encouraged continued trials. Within a year, such toxic reports

became less frequent (there had been a contaminant in the initial batch, it turned out) and soon motor rigidity, tremors, and then tardive dyskinesia (delayed abnormal rhythmic movements of mouth, tongue and facial muscles) dominated discussions of its risks.[12]

These motor signs were the fore-runners of the Parkinsonism and tardive dyskinesia that are hallmarks of chlorpromazine toxicity. Similar motor effects were soon reported forsuccessor neuroleptic drugs and motor inhibition became a marker of these agents. Decades later, the "atypical neuroleptics" were developed and promoted for their lesser motor effects with disregard for their lesser clinical efficacy. The NIMH-sponsored large clinical trial known as CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) undertaken in the 1990s randomly assigned patients either to the atypical neuroleptics olanzapine, quetiapine, risperidone, ziprasidone or to the typical neuroleptic perphenazine. The atypicals did not match the beneficial effects or cost-effectiveness of perphenazine. [13]

The EEG profile of chlorpromazine, we found in our studies, showed dose-related changes of reduced beta fast frequencies, increased theta slow frequencies, and occasional bursts of slow waves and spike activity. These rhythms heralded the seizures that became an acknowledged risk of the drug's use.

We had begun with 50mg doses but rapidly increased single dosing to 200mg and daily dosing to 1800mg. We learned that 1200 mg daily was effective and well tolerated in 80% of our subjects. These experiences led us to undertake two random controlled trials, one compared chlorpromazine to insulin coma and another comparing the effects of chlorpromazine, imipramine, and placebo in patients with a wide range of behaviors.

Chlorpromazine and Insulin Coma Random Controlled Trial.

A compelling motive for the comparison of chlorpromazine and insulin coma was the risks posed by the high doses of insulin. Seizures occurred in more than 10% of the sessions, and delayed spontaneous ("tardive") seizures often occurred late in the day or night, requiring additional intravenous or gavage dosing with glucose. For patients whose psychosis was responding slowly, electrically induced seizures were added at the height of the comas to augment the changes in behavior.

A "prolonged coma" was a much feared risk, the patient not becoming alert and oriented for many hours despite extensive dosing with intravenous and gavaged glucose. Many

explanations were considered and many interventions tested, but we did not find an effective treatment or method of prevention. We depended on intensive nursing care, repeated dosing with glucose, and monitoring until recovery. Two deaths in prolonged coma occurred in the five years that I supervised ICT at Hillside, a 2% mortality rate.

Sixty patients referred for ICT were randomized to receive either 50 insulin coma treatments or oral chlorpromazine (0.3 to 2.0 Gm/day; median 0.8 Gm/day) with both treatments given for a minimum of three months.Chlorpromazine treatment was as effective as insulin coma but with greater ease of use, greater patient comfort, lesser risks, and lesser expense—all clearly favoring chlorpromazine as a replacement for ICT. More than half of each sample improved sufficiently to return to their homes.[14]

These findings led to the closing of the insulin coma unit at Hillside Hospital in 1958, followed swiftly by other units throughout the nation. Within a decade the treatment had disappeared from American hospitals. A few units continued to treat patients with ICT as exemplified by the report that the 1994 Nobelist John Nash had received ICT in 1961 at Trenton State Hospital.[15] The treatment also persisted for decades in Russia and China, and was brought to Israel by Russian emigres.[16] My review in 2003 of what was known about insulin coma treatment, the lesser efficacy of ICT in treating psychosis and its increased efficacy with augmented electrical seizures led me to conclude that the spontaneous seizures were the basis for ICT's reported efficacy in relieving psychosis. ICT, to the extent it had therapeutic value, was simply a less efficient and more riskful form of convulsive therapy.[17]

The closing of the ICT unit was a heralded direct benefit the hospital gained from its support of clinical research.[18]

The Antidepressant Imipramine (Tofranil).

Among the new chemicals that gushed from industrial laboratories in those years, the antidepressant action of imipramine (Geigy 22355; Tofranil) interested us for the reports of the rapid relief in depressed, especially melancholic, patients. We selected agitated patients for dose-finding trials, finding that weekly dosing increases from 75 mg/day to 300 mg/day was an effective and safe regimen. While some patients became less depressed, others became more agitated and excited, slept poorly, with dry mouth and rapid heart rate. Older men had difficulty in urination. In our EEG studies, the changes in frequencies under the influence of imipramine

were distinguishable from the patterns of both chlorpromazine and ECT.[19] Its effects on different behaviors impressed us that imipramine was an active agent that differed from chlorpromazine.

Imipramine's EEG profile showed increases in both theta (4-7 Hz) and slow beta (13-18 Hz) frequencies, similar to anticholinergic drugs (diethazine, procyclidine and Ditran), patterns that were distinguishable from those of antipsychotic and sedative drugs. We had tested these anticholinergic agents in patients during their ECT course, when their behaviors had improved and the EEG showed high degrees of slow wave activity.[20] Similar EEG tests with imipramine, both orally and on intravenous administration elicited an EEG profile similar to that of anticholinergic compounds.[21] Since the pharmacology characteristic of these compounds was to inhibit acetylcholine, I became interested in the role of acetylcholine in the ECT process. Was the release of acetylcholine and increased levels in the cerebrospinal fluid essential to the therapeutic process of induced seizures? [22]

Our finding that imipramine blocked the EEG slowing of ECT led us to describe its central pharmacology as anticholinergic, a conclusion that was in conflict with the descriptions of pre-clinical studies in animals. Pharmacologists voiced doubts as to our results at a meeting organized by the pharmaceutical company Geigy in Montreal in 1958.[23] In time, however, the anticholinergic properties of imipramine in humans became recognized, and later was cited as a deterrent to its continued clinical use when other putative antidepressant drugs, such as the MAOI and SSRI agents, were being promoted by industry marketing. Considering the limited antidepressant efficacy of these later-introduced agents whose pharmacology was focused on serotonin and the greater efficacy of the tricyclic antidepressant agents of imipramine and amitryptyline, I conceived of a role for acetylcholine in the relief of melancholic depression.[24]

Chlorpromazine-Imipramine-Placebo Random Controlled Trial.

By 1958 we had developed effective dosing schedules for both chlorpromazine and imipramine in our psychotic and depressed patients. We were unsure, however, for whom to prescribe which agent. The conventional diagnostic schemata, either the classic Kraepelinian or the 1952 American Psychiatric Association DSM criteria based on psychodynamic descriptive principles, were of little help in prescribing the new psychoactive agents. We had confirmed the antipsychotic action of chlorpromazine and the relief of melancholic depression by imipramine. We had seen similar antidepressant benefits with chlorpromazine and were occasionally troubled

by excitement engendered by imipramine. Although the chemical structures of chlorpromazine and imipramine were much alike, we could distinguish the two drugs on EEG recordings but we had not yet shown which changes were related to which symptoms. We asked, for which illnesses and for which symptoms, was each agent effective?

We organized a random controlled trial in patients referred for medication treatments in a fixed dosing schedule for imipramine, chlorpromazine (combined with procyclidine to inhibit the rigidity and tremors associated with chlorpromazine use), and placebo. All medicines were given in the liquid vehicle that was used by the SKF pharmaceutical company to market chlorpromazine for liquid oral use, administered in fixed dosages on a three times daily schedule.[25] For two years, patients referred for medication treatment by the residents were randomly assigned to one of the three treatments independent of their presenting symptoms or history. All told, more than 150 patients were randomized to these treatments.

We described the clinical behaviors modified by the agents,[26] the changes in psychological tests,[27] and the distinguishing characterists in EEG studies.[28] Since no reliable diagnostic system existed at the onset of the study, we monitored the treatments weekly by scoring behaviors using individual items in the Lorr behavior rating scale and administered other neuropsychological tests before and during the sixth week of treatment.[29] Both imipramine and the chlorpromazine-procyclidine combination effectively relieved melancholic depression.[30] The profession had already characterized imipramine as antidepressant and chlorpromazine as antipsychotic. The efficacy of chlorpromazine-procyclidine in relieving psychotic depression was a new finding.

In anxious phobic adolescent patients, especially those with panic states, imipramine successfully resolved their anxieties. The finding contributed much to Donald Klein's later studies of anxiety states.[31] Among adolescents with psychosis, imipramine worsened their condition, a warning of a risk that had not been defined earlier.

Among ECT treated patients I had confirmed that the "language of denial" as described earlier by Weinstein and Kahn was a common feature among the patients with good outcomes. In collaboration with Robert Kahn, we described four patterns of adaptation to ECT that we labeled *euphoric-hypomanic, somatization, paranoid-withdrawal*, and *panic* modes.[32] We saw the associated behavioral changes as responses to the chemical changes in the brain, as non-specific (that is, not "antidepressant" in and of itself) changes in the behaviors affected by the

chemical changes. We thought it would be possible to find clusters of patients with similar brain chemistries that were similarly modified by imipramine.

We laid out the scores of the Lorr behavior items and calculated change scores for each of our treatments. With chlorpromazine, we identified eight behaviors in our subjects, some considered as "improved" and some as "unimproved." [33] No single identifiable behavior change seemed to characterize the reponse to chlorpromazine.

A similar analysis for the imipramine-treated patients identified seven behavior reactions including *mood elevation, explicit verbal denial, manic,reduction of episodic anxiety, agitated disorganization, anhedonic socialization,* and *non-response*. These reaction patterns were better descriptions of the responses to treatment than the conventional ratings of "improvement" and "non-improvement."[34]

We sought to relate the behavior changes following each treatment with the pre-treatment behavior styles. These views were based on the widespread belief that our patients' emotional illnesses were adaptations to life's stresses. Decades later, when a more systematic medical approach was applied to catatonia and melancholia as brain and body disorders, we did not consider these descriptions useful and did not undertake follow-up studies.

To identify characteristics of patients in the prescription of treatments, we developed a concept of "pharmacologic dissection," using the response to a medication to identify the underlying psychopathology. Thus, responders to lithium were seen as suffering from *mania*, responders to imipramine as *melancholic depressed*, and responders to chlorpromazine as *psychotic*. The model was useful when Michael Taylor and I later explored catatonia and melancholia, concluding that in both disorders patient recovery with ECT was the validation of each diagnosis.

While pharmacologic dissection is a conceptually promising way to identify clinical uses for the medicines, none of the medicine now in use has an identifiable biological relationship to a verifiable illness. Nor do the profusions of psychiatric labels for imagined illnesses that make up the DSM glossaries have definable relationships to measurable brain functions, nor to any defined behavior. Each marketed pharmaceutical was discovered by happenstance and no predictive brain measure or chemistry has defined any agent. The likelihood of using the response to a marketed drug today as identifying a specific psychopathology is remote. The trials to measure denial language after amobarbital by Weinstein and Kahn, or the EEG changes

and nystagmus after amobarbital in the sedation threshold tests of Charles Shagass, or the blood-pressure response to Mecholyl (methacholine) and epinephrine studied by Daniel Funkenstein, or the induction of panic by lactate infusion by Ferris Pitts and James McClure are, at best, physiologic effects that correlate with age and physiologic characteristics of the subjects. In our studies of the Funkenstein Test we found the changes in blood pressure to better correlate with patient age, not to any psychiatric behavior or to a measurable physiology. The best example of a diagnostic response to a chemical agent and behavior is the immediate relief of mutism, negativism, and posturing of catatonia with intravenous injection of amobarbital or a benzodiazepine, as we'll see in a later chapter. This response is so consistent it is considered a verification of the catatonia syndrome diagnosis.

In our dose-finding trials for imipramine weoptimized the dosing schedule to 75mg/day increasing in weekly 75mg steps to 300 mg/day. At these doses we observed behavioral improvements with few systemic complaints. When, however, the medication was withdrawn after the study period, within 48 hours patients complained of nausea, vomiting, dizziness, malaise and muscular pains.[35] The symptoms were first regarded as evidence of infectious illnesses but a review of the records in 45 patients found that these symptoms were better understood as physiologic withrawal. The symptoms were most severe in those treated for two months or longer. This 1961 report highlighted imipramine's dependence potential, adding imipramine to the CNS depressants, opiates, barbiturates, benzodiazepines, and alcohol that elicit tolerance and physiologic withdrawal after extended use.

The Hallucinogen LSD-25 and Chlorpromazine

The accidental discovery of lysergic acid diethylamide as a potent hallucinogen by a Swiss chemist is well known.[36] He described his experience as similar to a psychotic process. The manufacturer Sandoz was interested in having its actions tested and made samples freely available to investigators. Since it was projected as a new class of psychoactive drug with possible clinical use, we tested single intravenous doses of 10-50 μg in our patients, finding increased alertness and excitement. We did not observe the hallucinogenic properties that marked the enthusiastic street use of LSD. The EEG record in our subjects showed reduced amplitudes and increased fast frequencies, distinguishable from our other classes of agents. Single doses blocked the slowing and reduced the amplitudes in the EEG records during ECT,

eliciting increased vigilance and alertness and some complaints of discomfort. In single dose experiments the EEG effects of LSD were blocked by chlorpromazine.

Because we wanted to record the EEG effects in normal subjects we offered LSD-25 to our residents and staff members with a 6-hour observation period in the EEG laboratory. In 40 experiments we identified EEG patterns with reports of panic, nervousness, irritability, and increased color imagery. A single subject became paranoid, refusing to eat lunch despite my offer to eat the same foods that he ate. By the next day he was chagrined to have had the experience. A decade later we reported the EEG patterns of hallucinogens and deliriants in psychiatric patients, normal volunteers, and in post-ECT states.[37] We could distinguish compounds, like LSD and mescaline, with reports of illusions and sensory phenomena without clouding orientation or cognition. The anticholinergic agents atropine, scopolamine, diethazine, and Ditran elicited confusion and slowness of responses with increased slow waves and increased fast frequencies, which led us to cite these agents as deliriants.

A Soviet Psychiatrist Visits Hillside Hospital

With the sudden appearance and voice of Sputnik, the Russian satellite that circled the earth on October 4, 1957, a national outcry arose: another nation had been the first to launch a satellite into space orbit. How was it possible for the United States to be bested by the Soviets to "lose" the space race? As a researcher in biological psychiatry, I knew nothing of Soviet medicine; searching the literature to understand what scientists writing in languages we didn't know was impossible. We lacked an abstracting and translating information service. On November 15, 1957 the *New York Times* published my letter stressing that translations of abstracts and full articles from Soviet journals was needed for all branches of science.[38]

The response to this need across the sciences was swift. On January 14, 1958 the *New York Times* reported that the US Commerce Department had contracted with the National Science Foundation to translate Russian research articles and publish and distribute them to scientists.[39] For the next decade I received monthly booklets of translations of articles related to psychiatry. At first I read each issue avidly, and then with decreasing enthusiasm, as I found little that was useful in my work.

While we were in the midst of our research at Hillside in 1959 I received a surprise request from Nathan Kline, the psychopharmacology researcher at Rockland State Hospital who

had been one of the first to test chlorpromazine.[40] He had invited a visit by the leading Russian psychiatrist Andrei Vladimirovich Snezhnevsky, the Director of the Institute of Psychiatry of the USSR Academy of Medical Sciences. Snezhnevsky had conceived the illness of "*sluggish schizophrenia*," a diagnosis that labeled dissidents and political naysayers as psychotic, subject to hospital incarceration and forced treatment with neuroleptic drugs. Kline asked whether I would invite Snezhnevsky to visit my laboratories and associates at Hillside. As translator I invited Joseph Wortis, the scholar who had brought insulin coma to America and had written about his personal psychoanalysis with Sigmund Freud. We were not impressed by Snezhnevsky's explanations of sluggish schizophrenia and thought he was simply using his skills and authority to hospitalize dissidents.[41]

A few years later, in 1966, I sought an invitation to attend the Moscow meeting of the World Congress of Psychology and arranged a formal invitation from Prof Snezhnevsky. After many difficulties in obtaining visas, Martha, I, my son Jonathan and his friend Andrew Green, son of my Bellevue and Hillside colleague Martin A. Green, flew to Moscow via Vienna. The Russian presentations at the meetings were poor, confirming my opinion and those of my colleagues that Russian psychiatry merited little interest.

I sought to visit a leading Soviet electroencephalographer, whom I had met a year earlier in Vienna at an EEG congress, Natalia Petrovna Bekhtereva of the Leningrad Institute of Experimental Medicine, the daughter of Vladimir Bekhterev, a prominent Soviet psychologist who had developed similar views of behavior as conditioned reflexes as had Ivan Pavlov. At an earlier Vienna EEG Congress she had presented a plenary lecture on quantification of the EEG using the electronic filter analysis system of Grey Walter. As I was using the same analysis system I arranged a visit to her laboratory in Leningrad.

At the appointed time, I arrived in front of an imposing fortress-like building, fenced and dark, with front doors locked. I rang the Institute doorbell repeatedly, and after much delay a portly Russian woman in white nursing clothes with a large ring of keys came to the door. We communicated in German and she explained that Madame Bekhtereva was away. I showed her the signed invitation letter and she hesitantly opened the door and took me into the building, to meet two other women who reluctantly walked me through the Institute. Opening locked doors brought me to a large hall with some equipment and EEG drawings on the walls. The Grey Walter analyzer and a primitive EEG recording instrument were locked under a hood. A single

sample of a 30-second EEG and its analysis were on exhibit mid-room in a display case. I left, thanking the women and returned to my family. Bekhtereva, I realized, was a "show Soviet scientist," proffered at international meetings for her charm and family history.[42] Her contributions to science were minimal. From everything I was able to gather in subsequent years, the Soviet contributions to psychiatry and the disciplines of electroshock and EEG were trivial, a belief that remains true of Russian psychiatry in 2017.

08. Psychopharmacology: The St. Louis Interlude 1962-1966

In December 1961, I entertained a visit from George Ulett, with whom I had collaborated on quantitative EEG measures using the frequency analyzer that he built for me at Hillside Hospital in 1958, and on the role of anticholinergic drugs in the ECT process. A political crisis in the Missouri State mental health system, he said, had opened an opportunity for him to be appointed the Director in the Office of Mental Health. He had taken over a newly completed four-story 200-bed psychiatric hospital building on the grounds of the St. Louis State Hospital on Arsenal Street. The Governor had approved the creation of the Missouri Institute of Psychiatry, a research institute with a State budget. George had affiliated the Institute as a teaching and research center within the Department of Psychiatry at Washington University, and he offered me appointments as Director of the Institute and as Research Professor at the Medical School. The promise of a University affiliation, teaching medical students and residents, and affiliation with the Washington University Computing Center to develop digital computer programs to analyze EEG records for my patients enticed me and by July 1962, Martha, my children and I had moved to a new home in Lake Forest.

I had learned much about research methods, electroshock, and the new psychopharmacology in the 10 years I'd spent at Hillside. It was a golden period in biological psychiatric research, with human trials sanctioned, study funding readily available, and academic and public enthusiasm encouraging. The research department that I had established was next led by Donald Klein who developed a strong program in psychopharmacology. Although ECT continued as a clinical service, research studies of it ended for close to four decades until I brought the NIMH-supported CORE ECT studies to Hillside Hospital in 1997.

In the decade at Hillside Hospital with a large ongoing research program, we had few students. We were not related to a teaching institution, and we had little institutional support other than that of the clinicians on the hospital staff. Launching a new institute with large populations of severely ill as part of Washington University, with a spacious new physical facility and the promise of an expanding state budget, was seductive. The model in my mind was of the New York State Psychiatric Institute, an entity well supported by the State and academically strong in its connection to the Columbia University College of Physicians and Surgeons. I also expected that some of my Hillside Hospital associates would join me, though none did. They sensed the problems of a new adjustment better than did I. I was naïve in not

realizing that the physical distance from Arsenal Street to the University academic facilities at Renard Hospital, although but 15 minutes by car, would be an insurmountable hurdle for collaboration. Not having previously worked at a state psychiatric hospital I also did not realize the stigma associated with chronic psychosis nor the complex State politics involved in the budgets of such centers. Most patients were poor and friendless, with no community or political support. The negative attitudes toward the chronic psychiatric ill became clearer as deinstitutionalization became the watchword throughout the nation.

The Missouri Institute of Psychiatry (MIP) was dedicated in the Louis Kohler Building on Oct 22, 1962. The 4-story building had space for offices, laboratories, classrooms, and wards for up to 100 patients. The building was empty at its dedication, and I spent a busy year recruiting scientists and equipping offices and laboratories.[1]

My first Institute appointment was Nina Matheson as librarian.[2] In an era before the National Library of Medicine and the Medline program that began in the late 1960s, research centers developed on-site libraries. My personal collection of books, journals, and reprint files became the core of the MIP library.

I had catalogued my extensive collection of reprints measuring the changes in EEG associated with psychoactive drugs by author and by chemical agent. Thinking such a detailed review would be helpful to others, I submitted the list of articles and the indices to the editors of the *EEG Journal*. Without acknowledgement, a few months later I received page proofs for the journal supplement they had created from these files: *A Selected Bibliography of Electroencephalography in Human Psychopharmacology 1951-1962*.[3]

EEG Analysis at MIP. The Walter frequency analyzer was inherently unstable; it was very sensitive to room temperature and required daily calibration. Central to my move to St. Louis was the funding for exploration of digital computer analysis methods for EEG recordings in our medication studies. The promise of measuring EEG rhythms by digital computer methods was first announced in 1960, at the dedication of the Brain Research Institute at UCLA, where scientists from MIT analyzed a short strip of EEG using their digital computer.[4] Ten seconds of EEG were digitized and then analyzed by two statistical programs labeled power spectral density and period analysis. I attended that presentation and such studies were central to my St. Louis move.

In early 1963 I approached the computer center at Washington University to help me establish a center for EEG analysis at the MIP. Donald M. Shapiro, a doctoral candidate in digital computer processing, agreed to develop the computer programs.[5] In the Fall of 1964 an IBM 1710 digital computer with a central processor based on the IBM 1620 was installed. Over the next few years Shapiro developed signal processing programs to record EEG on digital tape, filter extraneous signals (noise), digitize the analog measurements, file the numeric values in the computer memory, and keypunch the data on Hollerith cards for statistical analysis. We developed four analysis programs, concluding that the baseline cross and power spectral analysis gave us the best measures of medication effects.[6] Some years later, we compared the relative merits of these methods of analysis, concluding that the methods offered analogous measurements. [7,8]

Computer-Based Studies. Once we developed an IBM 1710 computer center, in this era long before the advent of the internet, we catalogued and indexed each article to enable a quick search through our reprint collections. Other scientists in our group had their own collections, and these also were incorporated in the Library. Shapiro and the programmers developed computer search strategies for our reprints, a forerunner of the present National Library of Medicine and the Medline programs that are now universally available.

I had brought the electronic frequency analyzer Ulett had built to the MIP from Hillside Hospital and equipped two recording rooms as soon as I opened the Institute. In 1964, Turan Itil joined the Institute staff from Erlangen, Germany as head of the EEG Laboratories.[9] I had met Turan at the meetings in Florence, Italy, in 1958 of the Collegium Internationale Neuro-Psychopharmacologicum (CINP). He had also studied the EEG changes induced by chlorpromazine and imipramine in his patients, and when we compared our results, we discovered that our findings were the same, so much so that we could exchange slides for each of our presentations. We continued to collaborate, measuring the EEG effects of each new psychoactive agent. I had invited him to join me at Hillside in 1961 but migration issues and personal hurdles had delayed his move. Now he was able to join me in St. Louis in developing a pharmaco-EEG program with the support of the NIMH Early Clinical Drug Evaluation (ECDEU) program that I had moved from Hillside.[10]

By the mid-1960s interest in and study of new drugs dominated psychiatric research, and our work was no exception. A principal mission of the MIP was evaluating psychoactive drugs

for safety and efficacy. The NIMH moved quickly to support our institute's clinical ECDEU program as well as our special interest in EEG classification of new drugs.

Jonathan O. Cole, the head of the Psychopharmacology Service Center of NIMH, recommended we invite Samuel Gershon to join the institute's staff as pharmacologist.[11] Trained in Australia and an expert on the use of lithium in the treatment of mania, Gershon brought an interest in the actions of acetylcholine in behavior, inspired by studying the anticholinergic drug Ditran and the cholinomimetic agent tetrahydroaminacridine (THA). He developed animal testing facilities at the institute and appointed a team of collaborating pharmacologists and technicians.

Clinical Trials of Antipsychotic Agents. Within the first two years I had appointed clinicians to undertake clinical trials in the ECDEU program.[12] We developed study units to treat the chronic psychoses in the St Louis State Hospital wards and its outpatient clinics. The pharmaceutical industry was producing new agents rapidly and we studied the effects of promazine, thiothixene, fluphenazine, butaperazine, and the combination of thioridazine and chlordiazepoxide. Our interest in an injectable, long-acting form of fluphenazine decanoate led us organize out-patient clinics with scheduled visits for patients every 2 to 3 weeks.[13] The program was successful in reducing the number of relapses that required in-patient care.[14]

We tested a novel antipsychotic butaperazine and found it clinically effective. Itil had maintained a connection with the clinicians at the Bakirköy psychiatric hospital in Istanbul where he had studied. When he and I visited in 1963 we found the hospital wards filled with a multitude of patients with classical psychoses including screaming, restrained, and posturing catatonic patients. We negotiated a treatment trial for butaperazine to assess its efficacy and tolerability.[15] When we returned ten months later the change in the wards was striking: marked reductions in the use of restraints, aggressivity, and risks to the caretakers, testament to the behavioral benefits of new drugs.[16] A clinical trial of butaperazine in the Missouri hospital wards also found it more effective than chlorpromazine in controlling aggressive and destructive behaviors in a population of post-lobotomy patients.[17]

Leaving St. Louis. Our institute became a thriving research center, but then ran into a buzzsaw of shifting state politics and professional interests. Soon after my appointment at Washington University in 1961 the then Chairman of Psychiatry Edwin Gildea decided to retire.[18] In 1963, Eli Robins, Gildea's successor as Psychiatry Department chairperson, focused

the department's energies on student teaching, improving the psychiatry residency program, and biochemical research in the department laboratories.[19] The affiliation became moot for MIP as new appointments at Washinton University were refused. The schism between the MIP and Washington University sent Dr. Ulett to seek an affiliation for us with the Psychiatry Department at the University of Missouri in Columbia, about 125 miles away. While academic appointments were assured, the distance and the academic weakness of the research connections quickly led us to realize that the MIP could not assure itself of appropriate training of residents and medical students that were a mainstay of clinical research programs.

Furthermore, the MIP had been founded with the assurance of continuing Missouri state funding for the scientists and additional support from the community.[20] In the summer of 1964, Ulett announced that the state had not only not budgeted MIP financial support for the next biennium, but had also reduced our initial funding support--since we had been so successful in gaining our own outside funding.[21] The growth of the MIP was severely compromised and I and the other scientists saw little future for the Institute. The senior scientists and I quickly moved on.[22] Martha and I returned to New York by the Spring of 1966 with an appointment to the faculty of the New York Medical College with patient populations on the clinical services at Metropolitan Hospital in New York City.

In July 1966, we were happy to be leaving St Louis but we were anxious about resettling our children – Jonathan now age 15, Rachel age 10, and Linda age 8. We had lived in Great Neck during my days at Hillside, so a return there was logical. Some years after Martha's father died, her mother had remarried, and we were able to move into her now vacant house at 11 Bayview Avenue in Great Neck. A year later we bought our own home in Great Neck's Kensington Village.

09 Opioid Antagonists and Cannabis Studies at New York Medical College

Seeking to return to New York after my experience in St. Louis, I called on Alfred Freedman, chairman of the Department of Psychiatry at the New York Medical College. We recalled our days as residents at Bellevue, he in child psychiatry and I in neurology. It was the mid-1960s and among other cities, New York was flooded by opioid overdose deaths, by petty crime and robberies, and by widespread street sales of heroin, cannabis, and other Federally restricted drugs. A detoxification center was clearly needed as the city administration was in a panic at the rapid increase in deaths from opioid overdoses. Freedman was willing to undertake such a service at the Metropolitan Hospital, a large municipal hospital on East 96 Street and First Avenue in Manhattan, and asked whether I would direct the program.

"*I have no experience with opiate dependence or detoxification procedures*," I said.

"*We will learn together*," he replied, and we did.[1]

I was appointed Professor at the New York Medical College and at the end of the summer of 1966 I assumed responsibility for the Opioid Detoxification Service on the 15th Floor of Metropolitan Hospital. Within six months I had an EEG and physiology laboratory on the patient ward, and thereafter I split my time between the hospital where I taught residents and treated patients and the department office site at 5 East 102nd Street where my EEG research work was centered.

Donald Shapiro joined me from St. Louis, and in 1967, with NIMH funding, we leased an IBM-1800 computer that we programmed to quantify tape-recorded EEG records. While more stable than the Grey Walter frequency analyzer, this system was complex and required constant maintenance. In our psychopharmacology studies we measured the EEG to identify drug patterns, predict clinical uses, suggest effective dosage ranges, and relate the EEG changes to behavior. We also measured the time course of single dose effects and related them to drug and metabolite plasma levels. (See Chapter 9)

Heroin: Detoxification and Antagonists

Opioid dependence and overdose experiences with heroin, morphine, and methadone were the basis for admission to our Opioid Detoxification Service. Detoxification depended on skilled nursing care, maintaining fluid balance, and minimizing nausea, vomiting, and excitement. The literature had been filled with non-encouraging reports of detoxification trials

with the wide range of neuroleptics, barbiturates, benzodiazepines, and anticholinergic and antiepileptic drugs.[2]

In 1965 Vincent Dole and Marie Nyswander at the Rockefeller Hospital proposed substitution of methadone as a maintenance treatment to sustain opioid-addicted subjects within the community. Their thought was to administer a fixed dose of methadone daily, in a specialty clinic, expecting that the opioid will blockade any self-administered opioid and thereby minimize the need for street heroin.

Following their lead, we filed the necessary Investigational New Drug (IND) application with the FDA, overcame hospital-administration and public objections against prescribing heroin and methadone during detoxification treatment, and began dosage trials of methadone as a maintenance treatment. Methadone is less potent as a euphoriant, producing a lesser "high" than intravenous heroin. Its action of onset is slower and its duration longer. Daily administration blocks the acute euphoriant effects of intravenous heroin. The failure to achieve a "high" blocks the heroin effects that sustain continued dependence and use.

To continue a subject's interest in the painful process of heroin detoxification and treatment, the patient's membership in encouraging and supporting groups or families was necessary. A community treatment center for group therapy was set up by Richard Brotman at the College, while Richard Resnick [3]and Arthur Zaks [4] opened community offices for drug-dependent outpatients. By 1970, these active research and treatment programs put the college at the center of the national opiate dependence research and treatment.

Opiate antagonists. Abraham Wikler and William Martin at the Federal narcotic addiction center in Lexington, Kentucky had proposed the opiate antagonist cyclazocine, later naloxone, and then the longer acting opioid levomethadyl as maintenance treatments, similar to the use of methadone to block the euphoriant effects of opioids. They pictured opiate dependence as a conditioned response to repeated community stimuli and recommended trials of antagonists to serve as effective barriers to a resumption of opioid use and dependence. We undertook clinical trials and experiments with each of these substances in opioid-dependent inpatients on the hospital ward and in our EEG laboratory.

Heroin and Heroin Challenges. After subjects on the ward were detoxified with daily methadone, we asked for patient volunteers to study the degree of blockade to administered heroin by methadone, naltrexone, naloxone, and levomethadyl. "Heroin challenges" consisted of

first dosing with the antagonist and then, in the EEG laboratory, administering an intravenous dose of heroin with observations of the subject's self reports and changes in EEG, heart rate and pupillary size. Concentrations of heroin from 8 to 30 mg/ml in 1 to 2 cc of sterile water were tested before we settled on 15mg dosing as the standard challenge.[5] Diacetylmorphine (heroin) in pure white powder form was obtained from the ENDO Laboratories of Long Island with approval of the National Institute of Drug Abuse.[6] After laboratory experiments we measured the safety and acceptance of these agents and the duration of effective blockade to the subject's resumption of heroin use and the utility and safety of the drug in post-detoxification outpatient treatment.

Methadone and Heroin Maintenance. Patients tolerated methadone with minimal unpleasant effects. After detoxification, patients were advised that daily dosing with methadone was available at no cost in outpatient care, and that they would not experience the opioid "high" as long as they were taking daily methadone. In 16 subjects who had been inducted to methadone and discharged to the community, nine patients returned three times weekly for 12 to 21 months and were maintained on 75 to 130 mg methadone daily. Their social adjustment was equal to or better than that on admission, as seven worked steadily and one maintained his school enrollment. Seven methadone program patients relapsed. [7]

In another 29 subjects stabilized on 100mg to 300mg methadone, heroin challenges of 25 to 75 mg found full blockade to the "high" by EEG, heart rate and pupillary size criteria for up to 24 hours, with partial blockade to 48 hours. We settled on 100mg methadone daily as a useful dosing schedule in the community.[8]

When levomethadyl (LAAM), a long-acting form of methadone effective on oral dosing became available, we compared the duration of 30 to 80 mg taken orally three times a week to 100mg methadone daily. After six months, eight of ten methadone-treated patients and eight of nine LAAM-treated patients were undergoing continued treatment in the clinic. In patient acceptance, withdrawal symptoms, response to heroin challenges, and number of positive results for urine samples tested for morphine, the two groups were equivalent. We concluded that 80 mg LAAM administered three times per week is equivalent to daily administration of 100 mg of methadone hydrochloride.[9]

By 1972 the need for maintenance methadone treatment centers exceeded the supply. Few cities developed such treatment centers. Some authors recommended that heroin

maintenance treatment centers be established in which addicts could legally obtain daily intravenous heroin to sustain their habits under conditions that permitted their working in the community and maintaining a family. The treatment of opioid dependence was seen as akin to the treatment of diabetes. Since heroin use was governmentally restricted and eminently salable, however, it could not be made available in regular pharmacies on medical prescription. Vincent Dole voiced clinical and social objections to such trials.[10] I joined in his objection in a letter in which I described our difficulties with heroin injections citing EEG recorded seizure activity, transient tachycardia, irregular cardiac rhythms, unusually slow breathing rates, and stuporous states.[11]

At this writing in 2016, heroin abuse is again in epidemic proportions. In Vancouver, Canada a heroin maintenance treatment program is being tested. Its early reports are favorable. Similar maintenance programs have been active in the UK and Belgium.[12]

Cyclazocine Maintenance Trials. Cyclazocine is a narcotic antagonist that is well tolerated orally and was recommended as an alternative to methadone by William Martin. In the first 51 methadone detoxified heroin addicts in our clinic to whom we gave 4 mg/day cyclazocine, we were not encouraged by the high dropout rates and complaints of increased libido, constipation, insomnia, and restlessness. We interpreted these as withdrawal effects to the decreased use of opiates rather than direct effects of cyclazocine, the toxicity of which had been tested and not found in normal volunteers. A second group of 52 patients were studied in the EEG laboratory with gradual increased dosing of 0.2 mg, then 0.4 mg per day until a regular schedule of 4.0 mg/day was reached.

During these dosage trials in the EEG laboratory, intravenous heroin challenges of 8, 15 and 30 mg tested the degree of blockade at various times after cyclazocine dosing. In patients stabilized on 4 mg/day the blockade was demonstrated in EEG criteria and self-reports for up to 15mg heroin for 20 to 28 hours. Such experience encouraged us to undertake clinical outpatient trials in 52 patients. Thirty patients returned regularly to the clinic for up to a year's observation.[13] Once a stabilized induction and maintenance schedule was developed, outpatient clinical trials showed greater than 50% retention rates among these thirty patients for up to a year. Treatment continued at higher rates in the male patients in stabilized family settings, especially when wives participated in therapy sessions.[14]

Cyclazocine as a Clinical Antidepressant. In our EEG recordings of subjects with oral cyclazocine the pharmaco-EEG profile was similar to that of the tricyclic antidepressants imipramine and amitriptyline, leading me to ask whether cyclazocine could be an effective clinical antidepressant. I encouraged two clinical trials for antidepressant activity, one by Turan Itil in 10 hospitalized ill in St. Louis, and the second of 51 patients in the outpatient clinic at Metropolitan Hospital.[15] The daily dosage was 3 mg/day. Eight of the ten chronic non-addicted depressed ill that Itil studied showed at least a 50% reduction in depressive ratings within three weeks. Nineteen of the 51 outpatients reported reductions in depression symptoms. When cyclazocine dosing was ended, flu-like withdrawal effects were reported that were similar to those reported earlier for imipramine withdrawal, confirming the antidepressant-like action of the antagonist.[16] These clinical trials verifying antidepressant activity demonstrated, among other things that our quantitative EEG analysis was a useful predictor of psychoactive drug activity.

Naloxone Studies.[17] We obtained samples for testing of another heroin antagonist, naloxone, and undertook EEG trials. After heroin detoxification, we induced the typical mood and EEG effects of injected heroin (10-20mg) in volunteers. They were then injected with intravenous naloxone in doses of 0.7 to 10mg. With heroin, the addicts relaxed and reported positive feelings of a "high." When injected with naloxone, the feeling ended rapidly and the subjects became angry and hostile. They had experienced immediate and severe blockade of the systemic effects of heroin with withdrawal effects. With saline, the relaxation associated with the response to heroin continued for the remainder of the morning. Some subjects noted feelings of systemic warmth on naloxone dosing.

Oral naloxone had no effects on mood, behavior, or EEG in doses up to 100mg twice daily in detoxified addicts and in normal volunteers. In these trials we concluded that naloxone was a remarkably effective antagonist of immediate action but of short duration.[18]On our first clinical test in a patient stuporous in heroin overdose in the hospital Emergency Room late one afternoon an injection of 2 mg naloxone had him sitting up and responding within five minutes, a remarkable demonstration. I returned home, only to be recalled within an hour that he was somnolent again. Additional doses were administered with benefit and the patient was admitted for methadone detoxification. We established a protocol of multiple dosing of naloxone at 2-hour intervals for opiate overdose.

The heroin addiction crisis, once a scourge of young blacks and Hispanics in the cities has by 2016 become rampant among the white populations in the hinterlands of the nation. The crisis fills the daily news bulletins throughout the country. Naloxone is now formulated in a concentrated solution for intranasal use. Its safety has been assured. First responders, police, firefighters and EMT personnel are issued supplies for immediate use. The safety and efficacy of naloxone that we reported are now well confirmed by widespread clinical use with many life-saving stories.[19]

A Drug Treatment Center in Retrospect. My studies of heroin detoxification and of the efficacy and duration of narcotic blockade by methadone, levomethadyl, cyclazocine, and naloxone brought me face-to-face with the lawless world that resulted from the governmental criminalization of opioid drugs. Criminalization forces addicts to live in constant conflict with the police, to survive by lying and deceiving. The crisis was so severe that in 1973 New York State established the Rockefeller Drug Laws with extraordinarily severe penalties for drug sales. While the laws have had little effect on city crime, it materially increased the population of State prisons.

For the decades since I had become a licensed physician but before undertaking studies of opioids and cannabis, I had developed relationships of trust with patients and their families, expecting that answers to questions would be as honest as memory allowed. Dealing with addicts, however, taught me not to trust reports by the patients. The psychiatric examination depends on the symptoms reported by addicted patients. We developed random blood and urine testing to assess whether the subjects had reverted to drug use and to expect that they would not abide by dosing schedules.

On one occasion an oscilloscope was taken from the EEG laboratory at Metropolitan Hospital. I called the ward patients together and announced that all detoxification procedures were halted, and that methadone would not be administered until the instrument was returned. The next morning, an oscilloscope was standing outside the locked ward door. When I put the instrument in its carrier in the laboratory, I saw the label “Property of New York Hospital”--an instrument from another medical center had been stolen to replace the one taken from our laboratory.

On another occasion, I returned to my college office on 102nd Street after lunch and was met by two police (in raincoats to hide their guns--although it was not raining--just like the

images in Hollywood films) demanding that I come with them to their offices. No reason was given. I refused, they showed me their police badges, told me that I was under arrest, that the charge would be explained to me in due time. I went to the office of the department chairman, Alfred Freedman, who encouraged me (and my associate Arthur Zaks) to go with the men. We were taken by police car to the offices of the NYC Commissioner of Investigation John Murtaugh and assigned to wait in separate locked rooms. After an hour I demanded to be released, was shown the officer's gun and forced to wait. Finally, after a wait of almost two hours, I was escorted into a large office, with city, state, and national flags displayed behind a desk that dominated the room. A seated stenotypist and two police officers were in attendance.

The Commissioner charged me with possession and use of heroin and methadone. "*Of course*," I agreed. "*I study these substances in addicts*," I said, and announced that my possession of restricted drugs was legal, and that I was in charge of the research unit at Metropolitan Hospital.

"*So, you admit selling heroin*."

"*No, I do not sell heroin nor do I buy it. My supply comes from the Federal Bureau of Narcotics and Dangerous Drugs. I am a research physician and use heroin and antagonists in legal studies, supported by the City and State of New York, the NIMH, and the Federal Bureau of Narcotic D*rugs."

Disgustingly, Commissioner Murtaugh called Alfred Freedman, who verified my approvals and those of Dr. Zaks. We were told to leave. Demanding to be taken back to our offices, a police vehicle took us back. Being viewed and treated as a criminal was not appreciated.

The hospital authorities at Metropolitan Hospital (and later when I moved to the Northport Veterans Hospital) often questioned the justification for our studies and blocked requests to study our use of restricted drugs. They dreaded contact with addicts fearing, with much justification, attacks on their personnel and theft of the equipment and supplies. The drug-world is hostile, unpleasant, and threatening and the relationships antagonistic and outside my life experience. The described unpleasantries and many other threats and losses contributed to my later ready acceptance of a move and professorship at Stony Brook University in 1972.

Cannabis: Hashish and THC-Δ-9

In the spring of 1968, I received a call from Dr. Henry Brill, then director of the New York State Narcotic Control Commission, asking me to review the EEG records of chronic hashish users brought to his office by Professor C. J. Miras of Athens University, the head of that university's biochemistry department. Miras was growing cannabis plants, deriving hashish, and testing the potency of his samples by behavioral reports and physiologic measures in chronic hashish users. He had brought EEG records to New York for review, seeking professional opinions as to the normality or abnormality of the records.

Brill sent Prof Miras to my office with the records. I found them filled with continuous high-voltage, slow-wave activity that, if representative of alert adult subjects in an otherwise nontoxic state, would be considered evidence of chronic brain dysfunction. Brill visited Athens and confirmed that the subjects Miras was studying had been clinically awake and oriented, and without evidence of confusion, speech difficulty, or disorientation. He urged me to visit and make my own assessment.

The belief that cannabis plant materials, principally hashish and marijuana, were the introduction to heroin dependence was widespread and the alleged justification for the Federal criminalization of cannabis. I was as uncomfortable and as ill-acquainted with cannabis use and the marijuana world as I was with opioids, never having used it, but the possibility of measuring the changes in physiology and comparing U.S. and Greek users was enticing. Within my social culture, smoking marijuana or hashish was infrequent, its use considered dangerous as the gateway to more severe opiate and cocaine addictions. To my mind, the criminalization of cannabis, as that of alcohol and opioids, was a bizarre consequence of the Puritan religious heritage and a bizarre feature in America that had to be tolerated.

In May 1969 I visited Dr. Miras in Athens and met with three of his subjects, with Miras and an assistant translating. The subjects were cleanly dressed laborers in their late 30s, in good mood, well oriented, pleasantly answering questions about their work, family, and experience with drugs. They had been smoking hashish since early adolescence, two of the three were married and had children. I discerned no problems in speech, orientation, or movement that evidenced brain dysfunctions.

I visited the laboratories of the Athens University Psychiatry Department newly developed by Professor Costas Stefanis, finding them well equipped with EEG and

cardiovascular recording equipment. After assuring myself of Stefanis's interest in the research if we could get funding and approval, I proposed to Dr. Brill and to the NIH a collaborative study of the Greek hashish users and accompanying studies of cannabis users in New York City. Like our ongoing studies of opioids and their antagonists, I anticipated many problems in undertaking these studies, so sponsored them through a private, non-profit agency that had been supporting my electroshock and EEG studies rather than a public university or a city institution.[20]

Among our questions were these: Was hashish use accompanied by tolerance and dependence? Were brain functions as measured by quantitative EEG and neuropsychology tests abnormal? Were the widespread fears of "brain damage" an amotivational syndrome, antisocial behavior, and psychosis justified? And, what was the contribution of the chemical tetrahydrocannabinol-delta-9 (THC-Δ-9) that had been isolated from hashish in the Israeli laboratories of Rafael Mechoulam to the physiologic effects of Miras-supplied Greek hashish and American grown Federal BNDD-supplied marijuana?

Hashish users in Athens. Our source of 47 Athenian subjects was the population C.J. Miras had collected for his study of the effects of laboratory grown hashish.[21] The men were married Turkish immigrant dockworkers with families. A control group of 40 non-hashish users similar in background and history were referred by the users from among their friends. Both acute and chronic studies were undertaken with the subjects smoking Greek-grown hashish and US-imported marijuana cigarettes calibrated for THC-Δ-9 content.[22] In addition to acute single-day studies, 16 hashish users were observed on an in-patient hospital unit for six days, smoking US cannabis (marijuana) or Greek hashish or "placebo"cigarettes (having no cannabis content) for 3-day periods. Among the men in the experimental group their smoking hashish was daily practice encouraged by their family and accepted within the community. They would smoke on leaving for work and on returning home, with half the subjects reporting use during the working day as well.

Our psychological, EEG, and medical examinations found no abnormalities more prevalent in the experimental subjects than in the control subjects. Neither did the changes associated with acute administration of hashish, marijuana, and THC-Δ-9 differ. People in our sample were street savvy and competent, and we found no evidence of a chronic brain syndrome. The resting EEG records of the chronic users were normal in pattern, amplitudes, and frequency distribution. Four records of the 47 users (and 6 of the 40 controls), however, were considered

abnormal with higher percentage and amplitudes of theta activity. We did see occasional samples similar to those in the records Miras had gathered that sparked this study. The EEG slowing was of short duration, recorded soon after smoking hashish, and not dose related. Neither the EEG nor neurological examinations offered an explanation for the dissociation of the records and the observed behaviors. We could not identify an abnormal brain response, as all neurologic, psychologic, and repeat EEG studies showed no consistent abnormalities.

On smoking hashish, marijuana or THC-Δ-9, the EEG records showed an increase in amount and amplitude of alpha and theta frequencies, and a decrease in the beta and the average frequencies, that was dose related, with the maximum effect at 10 to 30 minutes, and return to baseline by 60 to 90 minutes. Pulse and breathing rates increased as did blood pressures. The self-reports of relaxation were dose related. The behavioral effects were correlated to the concentration of THC-Δ-9, making its examination a measure of potency.

In dose-finding hashish smoking (in oregano-tobacco cigarettes) at different concentrations up to 180 mg THC-Δ-9, the subjects evaluated doses over 100mg as "satisfactory" and relaxing and those lower than 80 mg as "unsatisfactory." In the experimental sessions, the three-day period of freely smoking oregano/tobacco-only was poorly tolerated. The subjects became irritable and demanded relief. The EEG, cardiac, breathing rate and other physiologic measures were dose related. The Greek users found the low doses that were tolerated by our New York subjects without effect, and expressed relaxation and physiologic effects only when dosages were over 100mg THC-Δ-9. We interpreted these findings as evidence of tolerance development with prolonged usage.

The examinations were undertaken jointly by members of the Greek and American faculties.[23] The Americans looked for specific evidence of abnormalities associated with hashish and could not find evidence to support the risk assessments often conjured in the United States at the time. The Greek observers believed that hashish use was a favorable aspect of the work and family activities of the Turkish smokers. But when the hashish smokers were compared to the controls that the smokers had recommended as colleagues, we could not define a consistent difference in family structure, work related behaviors, academic achievements, and systemic medical examinations between the two groups.

Our study was limited by the unique sample, but we had observed no signs of psychosis nor of an amotivational syndrome in the group. The subjects had achieved safe sources of

hashish and were able to maintain an active family and work life. Drug tolerance did develop with repeated use and social and physiologic withdrawal signs were evident in the withdrawal studies. Tolerance for high doses of THC-Δ-9 and the reports of their wives and family members that failure to smoke led to irritability and unprovoked anger supported tolerance development in chronic users. As with tobacco smoking and alcohol use, repeated cannabis use develops systemic tolerance.

Cannabis Physiology in New York subjects. We also studied the acute effects of marijuana and hashish in heroin addicts in post-methadone withdrawal states and in medical and college students who volunteered for experiments undertaken in the New York offices of the Department of Psychiatry at 5 East 102nd Street. All volunteers said that they had smoked marijuana before. Our laboratories were equipped for physiologic (EEG, blood pressure, heart rate) and psychological testing of memory, recall, reaction time in our ongoing pharmaco-EEG studies of experimental psychoactive drugs.

Although our studies were done with proper governmental and College approvals, we were repeatedly reminded that the substances were criminalized. Though more common in our opioid studies at Metropolitan Hospital, the staff of our department, particularly the clinicians actively maintaining post-withdrawal clinics in the same facilities, were critical that we were exposing volunteers to dangerous substances and risking addiction and dependence. The hashish samples Miras had given us and the marijuana samples from the BNDD were calibrated to the THC-Δ-9 content. Products in our study were smoked in tobacco cigarettes with oregano as a masking substance.[24]

The immediate awareness after inhalation of active cannabis substances was a feeling of relaxation, increased heart and breathing rates, and pupillary dilatation. Within two minutes the EEG showed an increase in amplitudes and appearance of theta frequencies, increasing over 20 to 30 minutes. The percentage of the time theta and alpha frequencies increased, disappearing over 20 minutes to a few hours after inhalation, depended on the content of THC-Δ-9. In some subjects, for short periods early in smoking, theta frequency bursts were observed. The onset of physiologic effects occurred within a few minutes of onset of smoking, dose-related in severity and in duration, usually disappearing within two hours. Short-term memory and reaction time tests showed parallel changes that were consistent with our studies of other psychoactive substances. In the context of pharmaco-EEG studies, the cannabis products were centrally

active, rapidly absorbed on inhalation, and quickly influenced the brain with consistent dosing effects. The THC-Δ-9 content marked the degree and duration of effect of each cannabis product.

Legalization of cannabis. We approached these studies with little experience with cannabis, anticipating that their use was dangerous with potentially severe social and brain-damaging characteristics. We confirmed that cannabis products affect the brain and induce body relaxation and that repeated use develops tolerance and discomfort on withdrawal. Cannabis is a centrally active substance similar in features to alcohol. We did not confirm fears of inducing psychosis, paranoia, social withdrawal and the rages of assassins that supported the nation's justification for criminalization of the substance and the severe punishments meted out to users and sellers. Parallel studies in Jamaica[25] and Costa Rica[26] supported by the National Institute of Drug Abuse (NIDA), came to the same conclusions, confirming earlier reports of the India Hemp Commission and the LaGuardia Commission.[27] Our studies did not support the social and legal criminalization of cannabis, hashish, or other hemp products.

Criminalization of alcohol use by the Federal constitutional amendment in 1918 had led to increased crime that eventually forced its legalization and the national availability of alcohol products. The price in inebriation, disease, accidents, family strife and deaths associated with today's alcohol use is a lesser price than the murder and mayhem rampant during the prohibition era. A similar change in the attitude toward cannabis appears to be underway as I write this note in January 2017, with 28 states and the District of Columbia having legalized the sale of marijuana for medical use and some even for personal use.

We did observe that the effects of marihuana and hashish on self reports of mood, heart rate, and EEG paralleled the concentration of THC-Δ-9. The THC was supplied by Dr. Rafael Mechoulam of the Hebrew University in Jerusalem.[28] Now that cannabis products are being openly sold in various States, it would be reasonable to make percentage concentrations of THC a standard reference for quality, much as the percentage concentration of alcohol is registered as the standard for beer, wine, whiskeys and other alcohol beverages.

More frightening is the widespread increase in opioid deaths, especially among youth in white communities. My experience in the 1960s and 1970s led me to favorably consider legalization of Federal scheduled drugs to reduce crime, shattered lives, prolonged imprisonment and death. Like legalization of alcohol, I expect the national price for legalization of opioid and

cannabis substances will be similar to that paid in legalization of alcohol, a much lesser price than the deaths, murders and imprisonments associated with the illegal activities that accompany the severe restrictions placed on opioid, cannabis, hallucinogens, and other proscribed drugs. The savings in shattered lives and excessive and expensive imprisonment surely justifies the legalization and sale of present scheduled drugs.

10 Quantitative EEG in Psychopharmacology

By 1954, the first clinical tests of chlorpromazine found it to be very effective in reducing aggression, excitement, and paranoid thoughts. As I introduced this experimental treatment on the wards of Hillside Hospital, I became enthusiastic about its very benefits, encouraged by nurses spontaneously referring their patients for its use. As some patients referred for insulin coma had been successfully treated with chlorpromazine, we organized a random assignment treatment trial comparing the two treatments, finding chlorpromazine to be as effective, safer, and much less expensive than the coma treatments.[1] The Hospital Directors closed the insulin coma treatment unit.

The EEG profile of chlorpromazine differed from that of amobarbital and ECT. The profile of imipramine (Tofranil, IMI), our next new agent, was also distinguishable from chlorpromazine. We puzzled, for whom should each medication be used? We organized a random assignment controlled trial comparing chlorpromazine, imipramine, and placebo, measuring behaviors, psychological test data, and changes in EEG. We randomly assigned each patient referred for medication treatment in the hospital to one of three fixed dose schedules regardless of symptom profile.

While the changes in EEG during the course of ECT were easily seen and readily measured by ruler and calipers, the changes accompanying the chemical agents were more subtle, the changes much smaller. We looked for a more sensitive quantitative measuring instrument and EEG quantification became our central interest.

*The Grey Walter Frequency Analyzer***.** During World War II the English physiologist Grey Walter at the Burden Neurological Institute developed an electronic frequency analyzer to measure the severity of head injuries. A single channel record, electronically filtered to minimize movement artefacts, was sent through a bank of 24 electronic filters, each tuned to respond to individual energies from 3 Hz to 33 Hz.[2]The premise of its military medical use was that increases in slow-waves were signs of brain dysfunction following trauma.

In 1957, George Ulett at Washington University described his use of a Grey Walter device[3] to measure the effects of atropine and scopolamine on the post-seizure EEG.[4] He quantified the changes in brain electrical energy as *mm pen deflections*within each frequency band and reported that both anticholinergic chemicals reduced the percentage time and the magnitude of high amplitude EEG slow waves induced by seizures.[5]

I visited Ulett in St Louis and was impressed that the device did quantify the drug-induced EEG changes. I received funding from NIMH and Ulett built a duplicate model for my studies at Hillside.[6] We obtained the instrument in the autumn of 1959 and used it in various studies, most prominently in the CPZ-IMI-PLO random assignment study. While CPZ enhanced the amplitudes and slowed the frequencies, imipramine increased the percent time of fast frequencies, distinguishing the brain effects of each agent.

*EEG Analysis by Digital Computer.*In 1960, at the dedication of the Brain Research Institute at UCLA, scientists from the Massachusetts Institute of Technology presented the analysis of a short EEG segment using digital computer programs.[7] The ten seconds of analog electrical activity were digitized and then measured by two statistical programs labeled power spectral density and period analysis.[8]

The Walter analyzer was inherently unstable and very sensitive to room temperature. It required daily calibration. I was impressed that digital computer analyses would be within the future for the analysis of psychoactive drug effects. Central to my move to St. Louis was my request for funding to explore digital computer analysis methods for the medication studies. In early 1963 I approached the computer center at Washington University to establish a laboratory for EEG analysis at the Missouri Institute of Psychiatry. Donald M. Shapiro, a doctoral candidate in digital computer processing, agreed to develop the computer programs. In the autumn of 1964 an IBM 1710 digital computer system with a central processor based on the IBM 1620 was installed at the MIP. Over the next few years Shapiro developed signal processing programs to record EEG on digital tape, filter electrical noise, digitize the analog measurements, file the numeric values in the computer memory, and keypunch the data on Hollerith cards for statistical analysis. After examining different analysis programs, concluded that the baseline cross and power spectral analysis gave us the best measures of medication effects.[9] Some years later, we compared the relative merits of these analysis methods, concluding that the methods offered useful analogous measurements. [10,11]

IBM-1800 Analysis System: In 1966 I moved to New York Medical College to study opioids, their antagonists, hashish, and marihuana, and to undertake new studies of ECT. Donald Shapiro joined me, and in 1967, with NIMH funding we leased an IBM-1800 computer system that we programmed to quantify tape-recorded EEG records. The programs for both power spectral density (Fourier) and period baseline cross analyses were developed and applied. This

system was complex and while more stable than the Grey Walter frequency analyzer, also required constant maintenance. Yet, we were enabled to quantify the EEG changes, identify drug-related patterns, predict their clinical uses, suggest effective dosage ranges, and relate the EEG changes to behavior. We also measured the time course of single dose effects and related them to drug and metabolite plasma levels.[12]

Following the introduction of chlorpromazine, then its congeners, and then different agents related to imipramine, came a flood of putative psychoactive drugs from industry laboratories. Psychopharmacologists were busy testing their effects on physiology and behavior in animal species. How to find new chemical entities with defined behavioral effects in man became an overriding question. Testing drugs in mice and rats identified animal toxicity. Phase-1 human toxicity trials in volunteers guided clinical use and safety. But what measures could be markers for antipsychotic, antidepressant, or anxiolytic potential? While a broad science of animal pharmacology catalogued the physiologic and behavioral effects of known psychoactive agents, did such studies predict the effects of new agents in man and in patients with different behaviors? Pharmacologists developed simple motor tests in animals responding to known chemicals, and then brought to human trial those agents that matched the pre-clinical response profiles of known drugs. Scientists at each pharmaceutical company tested their chemicals in rabbits, mice, rats, cats, guinea pigs, and occasionally in monkeys and chimpanzees. But their predictions did poorly when tested in the clinic. Although proposed agents matched known active agents in the pre-clinical animal trials, many failed in the clinic. Human trials became necessary to identify the association between the tests in animals and in man. Clinicians in the NIMH supported ECDEU program studied different physiology measures as markers for the effects in patients.

In the Hillside CPZ-IMI-PLO trial, we had distinguished the EEG, physiologic, psychologic and behavioral effects of the active agents, seeing each as profiles of the classes of antipsychotic and antidepressant agents. We tested amobarbital and amphetamine, then the new compounds megimide and fenfluramine. The novel anticholinergic diethazine very rapidly desynchronized the slow waves developed during ECT. Study of this compound and other experimental anticholinegic drugs led to our hypothesis of a cholinergic basis for the clinical effects of induced seizures.[13]

Soon, the flood of psychoactive agents that were being prescribed in diverse patterns to our hospitalized psychiatric patients elicited complex baseline EEG patterns. The effects of each agent persisted for days and weeks, husbanded in body tissues and slowly leached out and metabolized in time. Each exposure altered the brain patterns in complex, difficult to define ways. We could no longer find "a clean head" in which to measure a new agent's effect. We sought to test agents in prisoners, and came into conflict with changing concepts of ethics in human research. Prisoners were not "free agents" and, although we were careful to assure that their participation had only a monetary award and no change in their civil penalty, we were discouraged from such use.[14] In New York we studied new drugs in healthy male volunteers, paying for their hourly participation.

The digital computer system offered quantitative measures of frequency and amplitude changes with each agent. We developed EEG criteria for antipsychotic, antidepressant, stimulant, and sedative drugs using the effects of chlorpromazine, imipramine, amobarbital, and amphetamine as guides.[15] We also identified patterns for hallucinogens (LSD, mescaline), deliriants (atropine, scopolamine, diethazine), opioids (heroin, methadone, levomethadyl), their antagonists (naloxone, cyclazocine), marijuana, hashish and Δ-9-tetrahydrocannabinol, and a miscellany of agents with reported behavioral effects including phenytoin, aspirin, diphenhydramine, and novel peptides

Lessons Learned

Over the three decades of activity, we profiled agents that were clinically active and some subsequently marketed,[16] measured the relative potency and dosage ranges of sedative and stimulant drugs to guide clinical use,[17] examined the psychoactive properties of marketed agents in the search for a new useful chemical core,[18] and agents that showed little promise and were abandoned.[19] In some instances the EEG profile was instrumental in predicting effective clinical uses and dosage ranges and targeting marketing applications.

Doxepin (Sinequan). Based on its chemistry and its effects in animal tests Pfizer pharmacologists recommended this tetracyclic compound for clinical trials as an anxiolytic. After a year in clinical trials with a lack of an observable benefit in anxious patients, investigators met at the company's offices in Groton, CT to review the experience. A pall hung over the discussions until three investigators, Turan Itil, Herman Denber and I offered

understanding from our EEG studies. We failed to find the patterns of anxiolytic drugs, but did see changes similar to those of the antidepressant imipramine. We recommended doxepin be tested in depressed patients. Guided by our findings, doxepin was clinically tested and was quickly reported effective in depressed patients. It was successfully marketed as an antidepressant.

Mianserin (Tolvon, GB-94) was developed by the Dutch company Organon and recommended for a use in treating migraine. The research director, Theodor (Jack) Vossenaar,[20] sent the compound for EEG assessment to Turan Itil in St. Louis who reported its EEG profile to be most similar to that of amitriptyline. Because the pharmacologists considered the finding inconsistent with their experience as a serotonin and histamine antagonist, Vossenaar asked me to replicate the EEG study. I quickly confirmed Itil's finding and the subsequent clinical testing and marketing in Europe and Asia as an antidepressant was medically and economically successful.[21] I became invested in the EEG-mianserin story and presented the findings in many venues.[22]

6-azamianserin (mirtazapine). Mirtazapine, chemically related to mianserin, is a racemic mixture. In preclinical chemical and animal studies, the dextro-enantiomer was reported to be active and the laevo-enantiomer inactive. We examined the EEG profiles of both enantiomers and found no difference between them in the magnitude of the EEG changes with a pattern most similar to that of mianserin. Clinical trials for each enantiomer found both to be clinically effective although neither differed from placebo at the tested doses. The racemic mixture was successfully marketed as the antidepressant Remeron in the1990's.

Flutroline. Pharmacologic studies in dogs reported that a single 1-mg dose of flutroline inhibited the vomiting induced by apomorphine for as long as one week. Extrapolated to man, pharmacologists enthused that flutroline would be an ideal antipsychotic, requiring a single oral dose each week, pictured as the "Saturday night pill." In our clinical trials in actively psychotic patients we failed to elicit an antipsychotic effect, even at multiple and higher dosing schedules than initially recommended. EEG measures in our volunteers also failed to show a measurable change. The preclinical prediction of small doses being effective for days or weeks was untenable and studies of the drug ended.[23]

Aspirin, Anticonvulsants, Antihistaminics. We looked at commonly marketed agents with reputed behavioral effects seeking potential alternative clinical uses in their EEG profiles.

Acetylsalicylic acid (Aspirin) was occasionally reported to be soporific at its common dosing of two tablets each at .0325 Gm. We tested single doses of 0.65, 1.95 and 3.6 Gm in healthy adult men. The two higher doses elicited quantitative EEG, symptom reports, and cognitive functions characteristic of soporifics. Doses of 0.65 Gm were similar in direction and pattern but failed tests of significance.[24]

We sought to measure the basis for reports of changes in mood with the anticonvulsant phenytoin, finding the EEG patterns to mimic those of antidepressant drugs. The dosages for clinical benefit were high, so high as to risk toxicity. [25]

In an enthusiasm for peptides following the identification of euphoriant effects of beta-endorphin, we examined the effects of the peptides $ACTH_{4-10}$ and des-Tyr-gamma-endorphin. We could not elicit systematic EEG changes at the dosages and the parenteral routes that we were advised to use based on pre-clinical trials.[26]

The sedative effects of antihistaminic agents were well documented. Diphenhydramine and terfenadine elicited soporific, not antidepressant or anxiolytic patterns, and were not tested further.[27]

Opioids and Cannabis. The same principles of EEG study of new agents were applied to opioids and their antagonists, and hashish, marihuana and THC-Δ-9. We defined the EEG and behavior profiles of the compounds and measured the speed with which the antagonists blocked the effects of heroin and levomethadyl. In studies of marihuana and hashish the behavior and EEG effects were consistent with THC-Δ-9 content.

The Association/Dissociation EEG Controversy.

Industry searches for new agents with potential for human benefit are commonly based on similarities in chemical structure and the effects in animal trials. Early in our EEG studies, beginning with chlorpromazine and imipramine, our descriptions of the effects in patients and normal volunteers differed from the reports of EEG studies in animals. At meetings of EEG and biological psychiatry societies, both Turan Itil and I were often criticized for reporting effects on behaviors and EEG that differed from those reported in the animal trials that had preceded our human studies. Changes in the resting alert EEG in patients and healthy volunteers had elicited drug specific changes in frequency and amplitudes that we related to their clinical effects.

During the course of ECT, the frequencies slowed and amplitudes increased. During the ECT course some agents increased and others inhibited slowing, some increased fast frequencies, and some altered amplitudes. The post-ECT EEG became a sensitive index of brain function that varied in response to the chemistry of the tested medication. These studies had been done at Hillside Hospital in the 1950s.

Diethazine had been a new agent with well-defined anticholinergic properties that we administered to our patients during an ECT course. In post-seizure recordings with slowed EEG frequencies and increased amplitudes, intravenous diethazine sharply and quickly reduced amplitudes and increased the mean frequencies. The patients became agitated, depressed, and reported their pre-ECT symptoms. We inferred that seizures liberated free acetylcholine in brain and CSF and increased concentration of brain cholinesterases. These observations led me to suggest a cholinergic explanation of the ECT mechanism.[28]

Replications of the same effect with Ditran and experimental anticholinergic drugs of the JB series assured us of this pharmacology. When we measured the EEG effects of imipramine in our patients, in volunteers and in ECT patients, we found the same changes as we had seen with the anticholinergic agents. We inferred that imipramine blocked free brain acetylcholine, a finding that was inconsistent with its inferred pharmacology.

At a Montreal conference in 1969, my suggestion of imipramine's anticholinergic activity was criticized since such effects had not been observed in animals. The pharmacologists insisted that imipramine lacked such effects.[29] In time the anticholinergic effects of imipramine were increasingly recognized, even flouting this effect by marketeers seeking to replace imipramine with newer agents.

The next year, at the World Congress of Psychiatry also in Montreal, nine investigators from Europe and the United States, described their experiences with new psychoactive agents on the EEG and behavior. EEG changes characterized the qualities of psychoactive drugs – the defined changes predicted the behavior effects, and their absence identified clinically ineffective agents or ineffective dosing.[30]

Itil, I, and an increasing number of electroencephalographers studied drug-induced changes in human volunteers. As we described drug-related patterns that were clinically confirmed, greater interest in human screening of new clinical entities developed world-wide.

The study program that began at Hillside Hospital, flourished at my laboratories in St Louis and New York.

Many industrial pharmacologic laboratories established animal testing centers using implanted electrodes in diverse animal species. When pharmacologists assayed the EEG effects of putative and established new agents in rats, mice, rabbits, cats and dogs, results differed from parallel findings in human studies. The principal argument was made by Abraham Wikler who tested morphine, atropine, n-allylnormorphine and mescaline in dogs in slings. The animal EEG recordings showed sleep patterns; yet, their legs and eyes were moving rapidly.[3132] He concluded that there was a *dissociation between the behaviors and the EEGeffects*. His inference was supported by pharmacologists using other animal species. At an international conference of the CINP in Washington DC in 1968, the issue of pharmacologic "association" or "dissociation" was debated and resolved by the acknowledgement that the systemic and brain pharmacology of animals are not identical to that of man.[33] Indeed, an agent showing similar effects in an animal species and in man is a happenstance that cannot be predicted in advance. Preclinical studies in mice, rats, cats and dogs studies do not reliably predict drug effects in humans.

We had our own experience with the differences between the behavioral effects of drugs in animals and in man in St. Louis in the mid-1960s. Sam Gershon had trained in Australia and studied lithium in the treatment of mania. On the advice of Jonathan O. Cole, I invited him to join the MIP staff as pharmacologist. He brought an interest in the actions of acetylcholine, studying the anticholinergic drug Ditran and the cholinomimetic agent tetrahydroaminoacridine (THA). He developed animal testing facilities and appointed a team of collaborating pharmacologists and technicians.

His animal of interest was the beagle dog. One occasion, when Gershon was away from the Institute, the administrator asked me to approve the purchase of six setters as replacements for unavailable beagles from the animal breeder. The price for the setters would be the same. Not knowing of any difference between the species, thinking "a dog is a dog," I approved the purchase.

A few weeks later, Gershon complained that his anticholinergic drug experiments with setters failed to elicit the behaviors that were readily elicited in beagles. That the pharmacologic sensitivities varied among dog types as well as among animal species supported my argument that human trials were essential to understanding psychoactive drug effects.

The Pharmaco-EEG Paradigm

Whether the EEG and behavior of psychoactive drugs are "associated" and predictable in man as we maintained or were "dissociated" as pharmacologists asserted, clarified the pharmaco-EEG paradigm in clinical studies. Today's search for new psychoactive agents is rooted in the happenstance that chlorpromazine was a powerful sedative agent especially in paranoid, aggressive, hostile, and manic patients. Similarly, the antidepressant relief accorded by imipramine encouraged its trials in melancholic psychotic patients. These experiences invigorated a massive industrial investment, mainly in animal studies, with lesser expenditures in the clinics.

Much energy is being spent to find the effects of the agents on the brain's neurohumoral and neuroendocrine chemistry. Psychoactive substances alter behavior to the extent that they change brain chemistry. The pharmaco-EEG paradigm offers quantitative measures of these chemical changes that relate to their behavior effects. We are able to predict the changes in behaviors of psychosis, depression, or anxiety, elicit a delirium or reduce a manic episode, from the EEG changes. Failure to affect the EEG means that the agent has little effect on behavior, that it is behaviorally inert, and best marketed as a placebo.

Human studies are expensive and the science of pharmaco-EEG failed its promise and is no longer supported either in research laboratories or in individual patient care in clinics. Sadly, the same questions are now being asked in human studies using the present-day fashionable brain imaging methods with emphasis on concepts of connectivity and the size of brain nuclei. It is difficult to see such measures that are momentary images and not continuous as having more promise than that of pharmaco-EEG, which readily permits continuing assessments over time. Sadly, pharmaco-EEG in managing individual patients and in predicting the effects of chemical agents and physical treatments is a discarded science.

11 The Road to Catatonia

During my days in medical school and residency training I assume I was shown catatonic patients. Indeed, I recall walking through hospital wards, dressed in the short white coat of the student, with two 500 mg vials of Amytal sodium in one pocket, a metal autoclave box containing a sterile syringe and needles, a tourniquet and bottled water in the other, to sedate the excited and the manic and to relax the negativistic and the mute.[1] But during the decades of clinical practice as a research physician in New York and St. Louis hospitals, I cannot recall recognizing catatonia as a distinct syndrome. In my research positions, I had little front-line responsibility to examine and treat the acutely ill.

It was during my visit to the Bakirköy Hospital in Istanbul in 1965 that I saw nude women, standing in rigid Christ-like postures in hospital windows and rows of posturing men as we went through the wards. Catatonia is a systemic disorder of acute onset with mutism, posturing, rigidity, and stupor, and at other times as intense excitement and delirium. Patients remained ill for months and years filling long-stay hospital wards. Now, we have the technical means and the skill to recognize and treat these patients successfully and rapidly. Turan Itil, my research colleague at the MIP in St Louis, and I were visiting the Istanbul Bakirköy hospital to supervise a study of a new neuroleptic, butaperazine. Our arrival was welcomed by a patient band, colorfully dressed in 19th Century Turkish pantaloons and multicolored shirts, beating drums and cymbals, and playing the baglama string instruments -- an image of a mental hospital before the psychopharmacology era.

My enduring interest in catatonia was aroused some years later, when I became responsible for teaching students and supervising the care of acutely ill patients on the in-patient unit at University Hospital at Stony Brook in 1980. My experience with a fully restrained delirious woman and the remarkable resolution of her illness pointed me on the road taken.[2]

The Teaching Case

On a morning in the Fall of 1987 I was teaching an expert class in ECT when a patient from the medical service was referred for ECT evaluation. A class of five graduate physicians saw a restless, delirious and febrile 25-year-old woman in four-limb restraints, nasogastric and urinary catheters, and intravenous fluids running. When alert, she was negativistic, posturing, rhythmically thrashing, alternating mute and screaming. She was suffering the systemic disease

of lupus erythematosus, an acute autoimmune disease, being treated with intravenous methylprednisone for the lupus and sedated with haloperidol and lorazepam. An EEG had shown seizure-like activity and phenytoin was prescribed to block spontaneous seizures. She was in an acute manic and catatonic delirium.

Was she a candidate for ECT? The physicians, influenced by the severity of her systemic illness, the restraints, parenteral feeding, and manifest weight loss, thought not, that the treatment was likely to do her more harm. They demurred even after I described the rapid relief with ECT in three patients with the same psychiatric complications of lupus that had earlier been reported by Samuel Guze at Washington University.[3] Contrary to the class opinion, the severity of her excited illness supported treatment with ECT since the treatment was remarkably safe even in the most systemically ill patients.[4]

With consent of her family and her physicians, a course of ECT was begun on hospital day 28. Within 10 days and 7 treatments the delirium was relieved, restraints were lifted and cooperation improved. But family and physician fears and prejudices against continuing ECT forced me to stop her treatment, a decision that I strongly objected.

She regressed rapidly, again required restraints, and her family now pleaded for further treatment. A second ECT series from days 68 to 90 resolved her catatonic illness.[5] By day 100 she was discharged with medical relief of lupus and without signs of catatonia or delirium, to remain well and report the care of her family at one-year examination.

The severity and life-threatening nature of her illness, the rapid resolution with ECT, and my realization of her behaviors as "catatonia" intrigued me. Gregory Fricchione, then chief of Stony Brook's Consultation and Liaison Service and very experienced with catatonia, having developed the lorazepam treatment while studying at Boston's Massachusetts General Hospital,[6] had referred her for ECT after failed treatment with high doses of lorazepam. For the next few years we studied catatonia together. I became fascinated with the remarkable change from a delirious and moribund woman to a recovering mother with relief of a syndrome that I had hardly studied. I became interested in the story – how catatonia was discovered and described in Germany in 1874, how another German psychiatrist incorporated catatonia in his concept of schizophrenia that prevented much progress in its study.[7]

A Catatonia History.

In 1874 Karl Kahlbaum, the director of a private sanitarium in Görlitz, Germany, clustered peculiar motor behaviors of some of his patients into a single syndrome of "*Die Katatonie*."[8]In a rich text of 26 clinical vignettes, he clustered mutism, immobility, negativism, posturing, staring, grimacing, stereotypy, mannerisms, and several other motor signs as a single syndrome. The underlying illnesses that brought the patients for hospital care varied, with 12 patients severely depressed, 9 suffering from seizure disorders, 3 with neurosyphilis, and 2 with tuberculosis.He characterized the syndrome so well that within a few years many other physicians in Europe and America recognized his descriptions in their patients. (In a poignant final chapter of his book, Kahlbaum sadly notes that he could offer no useful treatment except to hope for spontaneous remission, which actually did occur in some cases. Death was all too common.)

By 1899 Emil Kraepelin, the German psychopathologist, teacher, and author of numerous textbooks, having recognized the same signs, published dramatic photographs of posturing and grimacing patients. He observed his chronic mentally ill patients for many years and characterized two principal syndromes. The patients with delusions, language difficulties, and hallucinations that began during adolescence and progressed to dementia were suffering from *dementia praecox*, he said. Those with depressed moods alternating with mania suffered from *manic-depressive illness*. Catatonia was seen in both groups. In later editions of his textbooks, Kraepelin described catatonia as a marker of dementia praecox.

This association of catatonia with dementia praecox was accepted by the Swiss psychiatrist Eugen Bleuler who relabeled the illness as *schizophrenia*. His approach was based on the beliefs of psychoanalysis, seeing catatonic symptoms as accessory manifestations of Freudian complexes, thereby marginalizing their importance in the diagnosis of schizophrenia for generations of psychiatrists, sidestepping the analysis of psychiatric nosology and obscuring efforts to conceptualize catatonia.[9]

When official classifications of psychiatric disorders by the American Psychiatric Association emerged in the 1950s, *schizophrenia, catatonic type* was the singular recognition for catatonia. This characterization dominated the psychiatric classifications during all of the 20th Century. It was this association that I was taught.

Treatments for Catatonia.

In 1930 William Bleckwenn, an American physician in Wisconsin, reported that catatonia could be relieved by injections of 2.0 or more grams of amobarbital (Amytal). Mute, staring, stuporous and posturing patients responded to injections by speaking, answering questions, and self-feeding. These changes were reported and also shown in a black-and-white film that was instrumental in launching the practice I was taught.[10]

A second effective treatment of catatonia, inducing grand mal seizures, came *de novo* into the world on January 2, 1934 when Ladislas Meduna, a Hungarian neuropsychiatrist, injected camphor-in-oil into the buttocks of chronic psychiatric ill at the Lipótmező sanitarium in Budapest. By happenstance, the majority of his patients exhibited the negativism, mutism, and motor abnormalities -- now considered signs of catatonia -- that were then considered signs of schizophrenia.[11] The method of induction was inefficient, eliciting a seizure in only one third of the subjects. Behaviors changed little but the few that did improve sufficiently impressed him to continue. Later that year he used a better method of intravenous injections of pentylenetetrazol (Metrazol), which elicited fuller and more reliable seizures.[12] The changes in behavior were so remarkable that he reported his cases in 1935 and again a year later at a meeting in Switzerland that canvassed experiences in new treatments of psychosis from 22 countries, setting the stage for worldwide interest in seizures as therapy.[13]Three years later he published his experience with 110 patients, reporting relief in more than half, especially among those acutely ill with catatonia.[14]

A year after that, the Italian physicians Ugo Cerletti and Luigi Bini demonstrated the same relief-inducing seizures using electricity rather than chemical injections. These treatments were remarkably successful in relieving catatonia, so much so, that once clinicians caught on, it was possible for a neurologist in 1981 to ask decades later, "Where have all the catatonics gone?"[15]

Catatonia Is Not Schizophrenia.

Awareness that catatonia was not limited to patients with schizophrenia came more slowly, however. By 1973, after examining the records of 2500 hospitalized patients with extended follow-up at the University of Iowa, James Morrison reported that 10% met criteria for

catatonia at their index admissions. Re-examination of the records of those patients at a later date found 40% had, at some point, recovered completely after treatment with sedative hypnotics or ECT.[16] Morrison argued that these recovered patients could not be examples of schizophrenia, a disorder for which treatments, at best, reduced the severity of symptoms but did not relieve the illness.

A year later Richard Abrams and Michael A.Taylor, two students from my classes at New York Medical College, identified 55 patients with one or more catatonia signs admitted to two wards at New York City's Metropolitan Hospital over a 14-month observation period. Only four patients among these satisfied the research diagnostic criteria for schizophrenia, while more than two-thirds met the criteria for affective disorders, usually mania.[17] They reported the salutary effects of treatments[18] and a factor analysis of the data identified two factors, one associated with mania and good outcome with treatment.[19]

That same year, Alan Gelenberg in Boston described eight patients who became toxic and febrile with severe Parkinsonian motor signs after receiving high potency neuroleptic drugs.[20] He cited the cases as instances of "the catatonic syndrome." In 1980, Stanley Caroff in Philadelphia, after describing 60 reported cases of neurotoxic responses to neuroleptic drugs, labeled an acute onset lethal catatonia syndrome with fever, autonomic instability, altered consciousness, stupor, and the rigidity and posturing signs of catatonia as the "neuroleptic malignant syndrome" (NMS), a label that was widely adopted.[21] He ascribed the syndrome to excessive dopamine blockade and prescribed dopamine agonists such as bromocriptine.[22] In time we learned that these treatments were ineffective, and they were replaced by lorazepam and ECT, the effective catatonia treatments today.

Is NMS a Form of Catatonia?

Recognition of the neuroleptic malignant syndrome came slowly into professional awareness. The occasional sudden death of a psychotic patient treated with chlorpromazine or other potent neuroleptic drugs raised little intellectual interest until the Caroff report appeared. After reading his description we at Stony Brook recognized three patients treated with neuroleptics who met his criteria for NMS. Repetitive motor movements, mutism, posturing, and negativism marked each story. We discontinued neuroleptic medications and, following Caroff's guide, prescribed bromocriptine. One patient responded slowly, but two did not. ECT

brought quick relief to them as well.[23] Although my curiosity about catatonia was not aroused until we treated the woman in delirious mania described earlier, we did find other cases of NMS.

At the height of the summer of 1976, a 23-year old agitated and aggressive psychotic man under my care at the Central Islip Psychiatric Center was refusing food and fluids and required restraint and sedation. Intramuscular haloperidol was administered. The ward was incredibly hot, he became dehydrated, febrile, suffered a seizure, became stuporous, and died within 12 hours. Neither physical nor psychological post-mortem reviews suggested a compelling reason. In retrospect, his acute death was an unrecognized example of NMS, the toxic syndrome associated with haloperidol that was waiting to be discovered.

Another example of NMS was the death of Libby Zion, an 18-year-old college student being treated for depressed mood with phenelzine. In the summer of 1984 she was admitted to New York Hospital febrile, agitated, and disoriented with abnormal motor movements. Meperidine was administered, her agitation worsened and parenteral haloperidol was added. Now in stupor, her temperature quickly rose to 107^{o}F and she died. Her family sued the hospital for malpractice and in 1993 I was asked to review the records as an expert witness in the hospital's defense. The many initial diagnoses did not consider NMS, but by the time of the legal case her experience was recognized as an example of neuroleptic-induced malignant catatonia.[24]

As NMS became increasingly recognized, various treatments were tested. By 1983 Gregory Fricchione described four cases in which high doses of lorazepam and withdrawal of the neuroleptic relieved the syndrome.[25] Case reports of lethal catatonia secondary to neuroleptic use followed quickly, each affirming the connection and citing relief with cessation of neuroleptic use and treatment with benzodiazepines and ECT.[262728] The significant connection between malignant catatonia and prior experience of catatonia was made by Denise White of South Africa who described five patients in whom the catatonia signs preceded the administration of a neuroleptic. In a second report a year later catatonia was presented as a precursor to the malignant state, raising the question as to whether the neuroleptic malignant syndrome, malignant catatonia, and the non-malignant forms of catatonia were manifestations of a single psychopathology.[29]

The acceptance of NMS as a form of catatonia was slow, inhibited by the different treatments offered. Stanley Caroff and his colleagues believed that NMS resulted from the

neuroleptic inhibition of dopamine activity and focused treatment with dopamine agonists bromocriptine and amantadine.[30] Because the fever, muscle rigidity, and weakness simulated malignant hyperthermia, they augmented treatment with the muscle relaxant dantrolene. Despite poor responses and continuing deaths, many authors applied this prescription. An international debate ensued, carried on for more than two decades, whether NMS was best considered an abnormality of dopamine metabolism and treated with dopamine agonists or an example of malignant catatonia and treated with benzodiazepines and ECT.[31] The debate argued at meetings of psychiatric societies and in the literature with Stanley Caroff, Gregory Fricchione, Steven Mann, Patricia Rosebush, Theresa Rummans, Michael Taylor, Gabor Ungvari, Denise White, and myself as the protagonists. The debates strengthened my interest in catatonia, and I adopted the view that NMS is best treated as a form of malignant catatonia.[3233]

Essential to the different views was the failure to recognize the signs of catatonia. For many observers the essence of NMS was the fever, autonomic instability, and muscle rigidity, encouraging belief in an overlap with malignant hyperthermia. Interest in catatonia was minimal, blocked by the prevailing belief that catatonia was schizophrenia, despite the reality that few NMS patients met the criteria for the thought disorder, impaired speech, delusions, and hallucinations that characterized schizophrenia. Further, treatments of NMS-classified patients with barbiturates and benzodiazepines were considered to risk tolerance development and dependence, beliefs that were substantiated by the FDA's restricted prescribing rules. Dosing was limited to a few milligrams of lorazepam, inadequate for the relief of catatonia. Few hospitals had ECT treatment units so clinicians could not prescribe this treatment--but all could prescribe dopamine agonists and dantrolene.

Then, in 1990, Michael Taylor presented a detailed argument distinguishing catatonia from schizophrenia in a historical and clinical review of its 100-year history.[34] He described both retarded and excited forms of catatonia and detailed effective treatments with barbiturates, benzodiazepines, and ECT. He connected the motor signs to the pathophysiology of the frontal lobes, presenting catatonia as an entity of many causes and many forms, thus challenging its consideration solely as a form of schizophrenia.

Simultaneously, the neurologist Daniel Rogers from the Burden Neurological Hospital in Bristol, England presented a similar challenge.[35] Of the100 chronic schizophrenic ill he had examined, many exhibited catatonia and Parkinsonism. Their presentations, though, were

similar to those that had occurred during the 1918 epidemic of encephalitis, which indicated that catatonia was not confined to schizophrenia. He described a systematic examination and a rating scale to identify catatonia, and he chastised psychiatrists who discarded the role of brain functions in psychiatric disorders.[36]

Both Taylor and Rogers questioned the Kraepelinian dictum that catatonia was a form of schizophrenia. Their doubts were consistent with my own that catatonia was not a marker of schizophrenia. That led me to argue for an independent status for catatonia in the classifications.[37]

The Drive to Systematic Recognition.

Was catatonia a singular identifiable disorder with common characteristics and homogeneous pathophysiology, or a galaxy of psychiatric aberrations with different pathologies? The 1980 DSM-III identified catatonia by the presence of at least one of the five signs of *stupor, negativism, rigidity, excitement*, or *posturing*. My Stony Brook colleagues culled the more detailed descriptions of catatonia signs by Kahlbaum, Kraepelin, Taylor, Rogers, Rosebush, and Lohr and Wisniewski to develop a 23-item list of identifiable signs scored on a 3-point scale and described a systematic examination that could be used to derive a diagnosis.[38]

Using that rating scale in 1994-5 we examined every patient admitted to our ward for catatonia signs. In potential catatonia cases, prescribed neuroleptics were quickly withdrawn, the effect of a single dose of intravenous lorazepam or diazepam was tested, and the patients treated with high doses of diazepam or lorazepam or with ECT.[39]

We next surveyed all patients admitted to the Psychiatric Service and the Psychiatric Emergency Room of University Hospital during a 6-month period using our rating scale. Of 215 patients examined, 9% had two or more signs of catatonia.

In the next year, of 470 patients examined we admitted 28 patients with four or more signs of catatonia to the in-patient service of University Hospital. Of these, 15 were affectively ill, 4 psychotic, 3 with NMS, and 6 with various systemic medical illnesses.

A review of the University Hospital records for the 5-year period beginning in 1985 with discharge diagnoses of schizophrenia, catatonic type (295.2) identified 43 charts. Of these, seven patients were also charted or discharged as *affective disorder*, five as *organic affective disorder*, and seven as *schizophrenia*. Eleven had been treated with ECT, with full relief in

eight, confirming again the remarkable efficacy of seizures to relieve catatonia.[40]

The Sedative Verification Test

Could the relief of catatonia's signs with intravenous lorazepam confirm the diagnosis even if it might not capture all cases of catatonia? Since William Bleckwenn had rapidly resolved catatonia with injections of amobarbital,[41] intravenous amobarbital had been widely used to gain speech for the mute, encourage feeding and toiletting in the negativistic, quiet the aggressive, and arouse the stuporous. In 1983 Gregory Fricchione recommended that amobarbital be replaced by lorazepam and that the reduction of catatonia signs be considered a verifying test for catatonia.[42] As verification of catatonia in patients with 2 or more catatonia signs for 24 hours or longer, we adopted the criterion of a 50% reduction in the catatonia rating scale score if it occurred within 10 minutes of the intravenous administrations of 1 to 2 mg lorazepam . The prescription of 3 mg/day of lorazepam, increased rapidly by 3 mg increments to 30 mg/day became our treatment protocol. Of 28 patients identified with catatonia signs, 23 recovered with lorazepam dosing alone, 5 did not. Of the four who consented to ECT, three recovered with 2 to 3 treatments, while one required 11 treatments. This experience was published in 1996 and the protocol became our standard diagnostic and treatment procedure; within a few years these methods had become widely adopted and central to the recommendations of the textbook of catatonia that Taylor and I published in 2003.

The Many Faces of Catatonia.

Beginning with our recognition of NMS, Michael Taylor and I soon identified other syndromes such as delirious mania, toxic serotonin syndrome, pervasive refusal syndrome, NDMAR encephalitis, Self-Injurious Behaviors in adolescents, and several other labeled syndromes that exhibited multiple signs of catatonia and were relieved by its known treatments. We thought that the syndromes must have a common pathophysiology since the signs were overlapping and the same treatments were effective.

Delirious mania. Catatonia is recognized in a sedated form of stupor, mutism, posturing, and negativism. It also is recognized in an excited, manic state. Catatonia is more often recognized among manic patients than among those with depressive moods or psychosis.[20,23-26,28] Among the patients admitted to our psychiatric facility so excited and overactive as to require

physical restraint, we increasingly recognized the signs of catatonia. Some vacillated between aggressive screaming and posturing mutely, with peculiar repetitive movements. Others were febrile, hypertensive and tachycardic. Some were delirious, all were confused and poorly oriented. Many had been treated with haloperidol or other high potency neuroleptics precipitating the malignant febrile form of illness. Some had seized and anticonvulsants had been prescribed.[43]

Many patients required four-limb restraints or were maintained in a padded isolation room. We withheld neuroleptics, prescribed high doses of parenteral benzodiazepines, and were often able to minimize the excitement. But the severity of the fever often forced more immediate treatment with ECT. A protocol of daily ECT found relief of excitement, delirium, and fever had occurred by the third day in almost every case.

Taking patients who are suffering a malignant systemic illness and subjecting them to the risks of anesthesia and induced seizures is counter-intuitive. But the fatality rate of febrile catatonia and the life-saving quality of the treatment was demonstrated in 1952 by Otto Arnold and H. Stepan who reported that daily ECT was often necessary.[44]They had treated 18 patients in their first clinic in 1947/48 with delayed treatments and 16 in their second 1949/50 with prompt treatments. Of the 18, 15 died and 3 survived; of the 16, 13 survived and 3 died, The lesson of daily or multiple seizures was learned, and I applied their experience on numerous occasions in patients with delirious mania or malignant catatonia.[45]

The Stony Brook hospital unit consists of rooms around a circular core. From the entrance to the ward it is possible to see the entrances to 3 to 5 rooms. I often came to the ward by 7 am, seeing a chair outside a room, with an aide watching the patient inside. These were the patients under 1:1 observation and care, often the most delirious and excited, or late adolescents with self-injurious behaviors. A 29-year-old HIV infected man had become severely depressed, suicidal, and delirious, refusing his HIV medications. In the ER, he was injected with haloperidol, became agitated and febrile. On the ward he was in 4-limb restraints, 1:1 observation, and parenteral fluids. After increased dosing with lorazepam with little response, we induced his first seizure. That afternoon he was out of restraints, only to relapse slowly. His temperature elevated and treatments were repeated on each of the next two days, with complete relief, cooperation and full self-care.

Two more examples. A 20-year-old college student was admitted in delirious excitement.

After 4 daily ECT sessions he was discharged to continue out-patient ECT for a total of 10 treatments. He completed his college courses. A 25-year-old musician in delirious mania was relieved by 5 daily ECT sessions, fully recovered by a full course of 12 treatments. Four years later, he was re-admitted after returning from an overseas working trip during which he had become exhausted. Again, daily ECT relieved the syndrome and he remained well.

In a review of the hospital records I found 9 additional patients with delirium, mania, and signs of catatonia who had responded well to ECT.[46] These experiences encouraged additional treatment of non-manic delirious patients and led me to recommend that ECT was an effective treatment for delirium, regardless of cause.[47]

An interesting misconception developed in the 1980s as the label "bipolar disorder" was popularized as a diagnosis after its delineation in DSM-IV. Depressed patients with a single manic episode in their history were labeled as suffering from bipolar disorder, neglecting possible catatonic features. The fashionable treatments for bipolar disorder span the breadth of the pharmacy, applying atypical antipsychotics, mood stabilizers, lithium, anticonvulsants, anxiolytics, sedatives, and antidepressants in complex combinations with notoriously poor outcomes.[48] As excited patients are forcefully restrained, treated with haloperidol and other potent neuroleptics, they rapidly develop seizures, fever, become mute, refuse fluids and food, become dehydrated and die, sometimes with fever and inanition or by improper tube feeding. Recognizing the signs of catatonia in severely manic and delirious patients and offering catatonia treatments is an unheralded aspect of the understanding of mania.[49]

But delirious mania is still not recognized in the revised nomenclature of DSM-5 published in 2013.[50] In his critique *What Psychiatry Left Out of DSM-5*, the historian Edward Shorter identifies delirious mania as just one of many illnesses that are not recognized. Michael Taylor makes the same observation in his personal history as researcher and clinician.[51]

Toxic serotonin syndrome. A 59-year-old married woman was admitted to University Hospital with a long history of treatment for mood disorder. Her most recent prescription had been the sedative trazodone at bedtime. She developed urinary incontinence and the serotonergic agent nortriptyline was prescribed. Within five hours after a single 25 mg dose, she became fearful, tremulous, sweating, tachycardic, hypertensive, incontinent of urine with explosive diarrhea. Four days later, she exhibited seizure-like movements of her extremities and lost consciousness. At the psychiatric emergency room she was mute, rigid, tremulous, tachycardic,

sweating, and hypertensive. The examination was consistent with NMS and lorazepam [1mg q6h] was prescribed, relieving the motor and vegetative signs within two days. She remained depressed and retarded, however, and responded well to ECT with lorazepam as continuation treatment.[52]

She had not been exposed to neuroleptic agents as her husband, a high school biology teacher insisted, showing his daily record of her symptoms and all administered medications. Toxic serotonin syndrome (TSS) is an acute change in mental status with systemic signs following the addition or increase in dose of a known serotonergic agent to an established psychoactive medication regimen. No effective treatment is known other than withdrawal of the precipitating medications and supportive care. The overlap in signs of toxic serotonin syndrome with NMS, and the successful response to catatonia treatments, argues that toxic serotonin syndrome is best considered and treated as a form of malignant catatonia.

Pervasive refusal syndrome. A syndrome described in the UK in 1991 meets our criteria for catatonia and represents another face of the syndrome.[53] Four British girls between the ages of 9 and 14 suffered "a profound and pervasive refusal to eat, drink, walk, talk or care of themselves in any way over a period of several months." They required nasogastric tube feeding and spent such prolonged periods in bed that they "occasionally requiring manipulations of the joints under general anesthetic to prevent contractures."[54] After extended hospital care and family and individual psychotherapies they eventually recovered.

A report of an 8-year old girl who stopped eating and drinking after a viral infection and who was hospitalized for more than a year before being returned to her family in partial remission was brought to my attention by Donald Klein; did she meet our criteria for catatonia, he wondered. We agreed that she did and asked the report's authors whether not testing and treating for catatonia was unethical. The authors offered a complex rejoinder without explaining the failure to test with barbiturates or benzodiazepines. [55]

A decade later I was consulted by the Irish child psychiatrist Fiona McNicholas about an 11-year old prepubertal girl who developed symptoms of asthma, abdominal pain, and insomnia. She refused to attend school or to eat or drink, became withdrawn and mute, and required nasogastric feeding and hospital care. After many months a video of her behavior was sent to me. Mutism, negativism, and posturing confirmed catatonia. Lorazepam testing and treatment was recommended. The parents refused medication treatments but participated in family

therapy. At first the girl took part but in time she refused. After 18 months of hospital care, as the date for her scheduled return home was imminent, she began to speak, eat and care for herself. Over the next six years she completed her schooling and went on to University.[56]

These cases are labeled "pervasive refusal syndrome." Less than 30 additional cases are cited in the literature, with a 3:1 ratio of girls to boys. Each reported case required prolonged hospital care. Similar cases are labeled "elective" or "selective mutism." The patients meet criteria for catatonia but it remains difficult for many physicians to consider catatonia except in the shadow of schizophrenia. The tragedy in each case is the availability of effective treatments and the clinicians' refusal to offer a proper diagnosis and effective care.

Recent descriptions of a "Resignation Syndrome"[57] among Syrian refugees in Sweden and a "Nodding Syndrome"[58] among children in the wars in Uganda find behaviors of withdrawal, mutism, loss of self-care, failure to feed that clearly mimic catatonia mutisms. Both these syndromes should be considered forms of catatonia. Such recognition would offer effective relief and bring these syndromes under the catatonia umbrella.

Anti-N-Methyl-D-Aspartate Receptor Encephalitis. A 2008 case report in the *New England Journal of Medicine* describes a 26-year-old woman admitted for headache, behavioral changes, abnormal movements, and mutism of seven weeks' duration. After extensive laboratory examinations a serum anti-NMDAR encephalitis test was reported positive, supporting the presence of an autoimmune disease. Throughout her illness she had been somnolent, mute, and negativistic, with repetitive movements of her arms and mouth, but these were not recognized nor treated as catatonia. An ovarian teratoma was found, surgically removed under anesthesia, and the encephalitis syndrome resolved within a day. Was the removal of the tumor or was the anesthesia the therapeutic agent? The rapidity of the resolution and her course favor the probability that catatonia was relieved by the anesthesia.[59]

Another report described a 16-year-old boy with protracted stupor, psychomotor retardation, mutism, posturing, stereotypical movement, refusal to eat and drink, and episodic agitation.[60] A positive blood test supported an anti-NMDAR diagnosis. The presence of catatonia was not recognized and no consideration given to its treatments. Instead, haloperidol and other antipsychotic agents were prescribed worsening the symptoms. After seven months of nursing care the illness abated. The experience was trumpeted as a clinical lesson in the

American Journal of Psychiatry despite the failure to recognize catatonia or to consider its treatment.[61]

The signs of catatonia were commonly described in a 2008 report of 100 cases of encephalitis with positive NMDAR serum tests, but neither catatonia nor its treatments were discussed.[62] Case reports now dot the literature with most patients being female and with resolution after resection of ovarian teratomas when found. But the syndrome is also reported in males and among many patients without evidence of tumors.[63] By 2013, five patients with NMDAR encephalitis had been successfully treated with ECT.[64]

Limbic encephalitis is an acute autoimmune neurological disorder first described in the 1960s as a 'paraneoplastic condition' – self-poisoning systemic changes induced by tumors. More than 80 different autoimmune disorders are described in the medical literature. The pathophysiology is poorly understood and the treatments are empiric and of limited efficacy.

The diagnosis of anti-NMDAR encephalitis depends on a positive serum or cerebrospinal fluid antibody test.[65] The recommended treatments are tumor resection when found and non-specific immunotherapy (corticosteroids, intravenous immunoglobulin or plasma exchange) or immunotherapy medications (cyclophosphamide or rituximab). These treatments have not been demonstrated to be effective and are associated with prolonged illness. My appreciation is that these patients have a systemic illness of acute onset, with a positive chemical test, with a high incidence of tumor, and frequently expressed as catatonia. Treatments for catatonia, when applied, have successfully relieved the illness.

A heightened enthusiasm for this diagnosis is reflected in an editorial in the *British Journal of Psychiatry* in April 2012 calling for laboratory tests for anti-NMDAR encephalitis in "all individuals with a first presentation of psychosis, or people with psychosis and features of autonomic disturbance, movement disorder, disorientation, seizures, hyponatraemia or rapid deterioration . . . with the possibility of antibody-mediated encephalitis in mind."[66]The recommendation continues: "This assessment should include, as a minimum, a neurological and cognitive examination and early serum testing for antibodies against the NMDA receptor and voltage-gated potassium channel. All patients testing positive for these serum antibodies should be referred to neurological centres with expertise in managing these cases."

The enthusiasm for this diagnosis is also illustrated by the rapidly increasing case-report literature. The initial references to anti-NMDAR encephalitis cited in Medline are in 2007. By

July 2014, the number had increased to 230 citations and by December 2015 had increased to 333. As with patients with pervasive refusal syndrome, recognizing catatonia in anti-NMDAR encephalitis offers effective treatment. It is reasonable to consider catatonia in the differential diagnosis and offer its tests and effective treatments but this is still too seldom done.

Self-injurious behaviors in mental retardation and autism. Patients identified in the past as suffering from mental retardation are now often discussed as examples of autism or autism spectrum disorders. Many such patients exhibit persistent repetitive movements, often screaming or hitting themselves. Such self-injurious behaviors cause much damage. Restraints, antipsychotic medications, and deconditioning procedures are poorly effective. Courses of ECT, however, markedly reduce the repetitive behaviors and many young patients have been returned to home and community.[67] They do require continuation ECT, however. A benefit of the success of these treatments has encouraged broader acceptance of ECT among child and adolescent psychiatrists.

Other repetitive behaviors in children and adolescents are recognized as obsessive compulsive disorder (OCD) and Gilles de la Tourette syndrome (GTS). These are commonplace among adolescents labeled as suffering autism or autism spectrum disorders.[68] A 2014 report describes an 18-year-old man with a 8-year history of progressively severe GTS that responded rapidly to ECT.[69] The scientific literature is speckled with incidental relief of GTS and OCD with ECT that encourages a more inclusive application of catatonia criteria to these syndromes with the application of catatonia treatments.

The DSM Classification Debates*: *Where Should Catatonia be Classified?

The initial classification of psychiatric disorders published by the American Psychiatric Association in 1952 was revised in 1968 and again in 1980. In each version catatonia was singularly recognized as *schizophrenia, catatonic type* (295.2), making catatonia signs markers of this broad class of psychosis and neglecting evidence of catatonia among other disorders. The catatonia-is-schizophrenia equation led physicians to prescribe neuroleptic drugs whenever catatonia signs were recognized. Such treatments were not only unhelpful, but they often precipitated a malignant neurotoxic state, worsening the illness, and occasionally causing death. Only when the clinician distinguished the signs of catatonia were the patients appropriately treated with barbiturates, benzodiazepines, and ECT. Taylor and I argued that it was necessary

to divorce Kraepelin's marriage of catatonia to schizophrenia and to recognize catatonia as a distinct, independent syndrome warranting a home of its own.[70,71]

The 1994 revision (DSM-IV) retained the five types of schizophrenia and added the independent class of "*catatonia secondary to a general medical condition*" (293.89).[72] I was pleased that an independent syndrome was recognized and hoped that such a designation would increase its recognition and encourage the prescription of effective treatments. Indeed, over the next two decades, recognition of catatonia increased and reports of malignant catatonia declined.

Another DSM revision was planned in 2008 with catatonia assigned for consideration in the Psychosis Work Group. By this time an extensive literature supporting catatonia as an independent entity had developed and a consortium of catatonia scholars that I led asked that the catatonia type of schizophrenia (295.2) be deleted and that catatonia be designated by a single code as a distinct, definable, and treatable syndrome.[73]The publication of DSM-5 in May 2013 deleted the class of schizophrenia, catatonic type (295.2); continued the class of catatonia secondary to a systemic medical condition (293.89); offered a class of "unspecified catatonia" (781.89); and included a "catatonia specifier," coded as xxx.x5, for ten principal disorders including depression, bipolar disorder, and schizophrenia types. (A specifier is a label added to a primary diagnosis to indicate a subtype of the primary diagnosis. It avoids a decision about which aspect of the behavior, the psychosis or the catatonia, is the verifiable diagnosis.)

The divorce of catatonia from schizophrenia has led many psychiatrists to an earlier prescription of effective treatments, lowering rates of chronic illness and death. Many variants of catatonia with unique effective treatments are now recognized.[74] Once considered rare, catatonia is now reported in about 10% of the populations admitted to psychiatric hospital units, assuring earlier recognition and more effective treatments.[75]

During these most recent DSM deliberations the initial debates occurred between classical scholars represented by Gabor Ungvari[76] and the catatonia scholars beginning with the work of Michael Taylor and Richard Abrams in 1970s. Ungvari supported the Kraepelin image of catatonia as the abnormal motor signs found among patients with chronic psychosis. He had treated hospitalized long-term Chinese ill in Hong Kong with lorazepam and saw little benefit, but he had not tested the benefits of electroshock. Modern scholars, however, are recognizing catatonia in acute treatment hospitals, finding many cases that meet the Kahlbaum criteria for catatonia. When Kraepelin identified catatonia in his chronically ill patients, he assumed that he

was describing the same syndrome. The experience of the DSM-I to DSM-III classifiers was with similar chronic hospitalized ill since their office practices of psychotherapy did not accept catatonic patients – those with mutism, negativism, and posturing, for example. By the time of DSM-IV's publication in 1994, however, some scholars had identified the catatonia described by Kahlbaum. Their experiences led to the addition of the special class of "catatonia secondary to a medical condition."

The connection of the catatonia scholars to the Psychosis Work Group was through Stephan Heckers, the chairman of Psychiatry at Vanderbilt University. That he accepted our picture of catatonia as an independent treatable syndrome is seen in his retrospective review published at the beginning of 2015. After examining 339 hospital charts, two or more signs of catatonia were recorded in 300 patients with 232 validated by positive relief with lorazepam treatment or ECT. The mean lorazepam dose was 6 mg/day with 84% responding. ECT was applied in 20% with 42 of 45 (93%) responding.[77] This independent verification of Taylor's and my image of catatonia was most welcome.

Present day understanding distinguishes the Kraepelin and Kahlbaum forms of the illness, one tied to chronicity and poor responsiveness and one accepted as the varied expression of acute, treatable illnesses.

A Catatonia Textbook.

Taylor and I decided to summarize our experience with catatonia and published *Catatonia: A Clinician's Guide to Diagnosis and Treatment*, a 256-page text in 2003.[78] At the same time we presented our experience in a review in the *American Journal of Psychiatry*.[79]

We see ourselves as clinicians, not laboratory scientists. We identify illnesses, use verifying tests, and explore effective treatments. We recognize that inducing seizures is a most remarkable and unique discovery in medicine, one that has been unfairly stigmatized by the professions of psychiatry and neurology as well as by the public. The science is poorly taught in medical schools and psychiatric residencies, many of which have no facility for its use, thereby denying relief to many of the mentally ill who they serve.

Since that publication we have explored catatonia further. A decade later it seemed timely to bring our knowledge up-to-date and I published a review as a supplement to the *Acta Psychiatrica Scandinavica*.[80] It is a biography of the syndrome, how it was developed, its early

exploration, the incorporation in schizophrenia, and its rediscovery as a definable distinct entity. The essay reviews the arguments about its classification, and the new forms that are recognized.

It also discusses an interesting association with animal tonic immobility, a defense described in prey animals. Many catatonia signs – stupor, mutism, posturing, repetitive behaviors – are characterisic of animals when they find a predator in their neighborhood, and I suggest that catatonia is a relic of human biologic history. Subsequently, I have argued that catatonia is an atavism, a relic of the past when *Homo sapiens* was both predator and prey, with the defenses of flight, fight, and dissimulation that are retained today. [81]

The Catatonia History.

The remarkable story of catatonia enticed the medical historian Edward Shorter and we agreed to write this history. We had worked together to write and publish the history of the syndrome of melancholia[82], and had collaborated in the studies of catatonia. As the chapters of the history unfolded, we became increasingly impressed that each observer, beginning with Kahlbaum, reported the remarkably state of Fear as central to each patient's description. In contrast to most systemic illnesses, that leave evidence of tissue and physiologic damage after relief is assured, patients after catatonia exhibit no residua. We began to see the behaviors of catatonia as akin to physiologic events as crying, sneezing and coughing. As we wrote we soon titled the story as *The Madness of Fear: A History of Catatonia.* The book was published in May 2018 by Oxford University Press. [83]

Epilogue

My colleague Michael Taylor, after reviewing his decades of psychiatric research, sorrowfully concluded that the profession of psychiatry still has little understanding of mental illnesses and continues to disregard the role of the brain in the disorders that are seen by psychiatrists in their offices and clinics.[1]Hippocrates of Ancient Greece, the esteemed Father of our profession, is crying at our disarray, in our enthusiasm for a meaningless philosophy of psychodynamics, our disinterest in the role of the brain in behavior, and in the distancing of the discipline's practice and teaching from that of clinical medicine. My experiences have been very similar to his, yet I believe that we (Taylor, our colleagues, and I) leave our discipline slightly better in its skills and understanding, and although Hippocrates would surely cry, he will also smile for a few new skills that we and our colleagues have added to our practice.

Surely, the continuing interest in and use of electroshock therapy as the treatment for severe depression, mania, psychosis and catatonia, still increasing worldwide use after 80 years, is a much unheralded and stigmatized practice that continues to benefit many seriously ill and to save lives. We did much to optimize the treatments so that we know how to effectively relieve patients suffering from severe disorders in 3 to 4 weeks or sooner, to do so safely without fear of death or fracture or persistent confusion – signs common in the first decades of the treatment's use. Patients return willingly, knowing that the worst is the painful skin puncture for an intravenous line.

A sad aspect is the overwhelming allegiance given by the psychiatric discipline's leaders to psychotherapy and pharmacotherapy. Their ignorance of electroshock precludes the education of medical students and psychiatric residents. Few physicians learn about the merits of induced seizures in patient care in medical school or residencies. Those who use the treatment need to develop skills considerably beyond the longstanding practice of "see one, do one, teach one" of the first decades of ECT's use. The failure of the psychiatric educators to insist that psychiatrists learn this skill is shameful.

As a clinician and investigator I have supported the treatment throughout my professional life. I have optimized the practice, educated the profession and patients and their families, and offered explanations to ease the anxieties generated by the name "shock therapy" and the apprehensions generated by Hollywood films and anti-ECT professionals and public. I have

written guidebooks for patients and their families and published a 22-minute videotape that is shown to patients during the consent process.

The EEG recordings now incorporated in the devices used in treatments are the best guide to effective treatment. I developed digital computer programs to quantify the recordings and the audible EEG, which offers treating doctors a warble sound that tells them what is happening in the brain so they can judge the sufficiency of the seizure.

At least three times I have carefully investigated and found that treatments that are given through unilateral electrodes to be less effective than those through bilateral placements. I believe their use today is not justified by the temporary reduction in confusion during the treatment course. I see such use unethical, except in the elderly depressed who can be saved the embarrassment of incontinence and temporary confusion.

Insulin coma therapy was an alternative seizure method. The random-assignment study with chlorpromazine showed the medicine to be as effective and much safer than insulin coma therapy, ending its use. I have argued that the non-seizure neurostimulation technologies of rTMS, VNS, tDCS introduced as replacement for ECT are not effective and are not useful alternatives. The central event in ECT is the induction of the seizure, the element that cannot be accomplished by any of these devices.

I described the neuroendocrine explanation of the mechanism of the seizure and that explanation holds today as the most supported theory of the treatment's efficacy. I created the scientific *Journal of ECT* that publishes the principal contributions to the science. It is in its 33rd year of successful publication.

I have taught many physicians the skills of the treatment and mentored numerous researchers.

In the 1980s, as a clinician at the University Hospital at Stony Brook University Medical School I became active in treating patients in the hospital and teaching medical students and psychiatric residents their skills. It was a return from my Hillside days, and the primary patient contact it entailed brought many illnesses to my attention. I had been taught that catatonia was a form of schizophrenia and found many signs of catatonia in patients with mood disorders and the systemically ill in the hospital. I sought out such patients and learned how to identify their illnesses, to verify it by the quick relief given by a sedative barbiturate or benzodiazepine medication, and most importantly, how to effectively treat catatonia by high doses of

benzodiazepines or by inducing seizures. The success of these treatments is remarkable, with almost all patients recovering from their illness.

Catatonia is a syndrome of mutism, negativism, posturing, rigidity and other motor signs that was thought to be a form of schizophrenia, but as many have shown, it is a systemic condition of acute onset, that appears in many guises. The common sedated mute patient whose condition is known as Kahlbaum's catatonia may also appear in a very excited state of "delirious mania," or in a febrile toxic state of "malignant catatonia," or as one of many mutisms, or as the self-injurious behaviors of adolescents. Each of these variants have been described with Michael Taylor in our textbook in 2003.

I led the profession to discard the classification of catatonia only as a form of schizophrenia and to have catatonia classified and regarded as an independent syndrome acknowledged in the official classification by the American Psychiatric Association in 2013. In systematic studies I have shown catatonia to be found in about 10% of hospitalized patients in academic general hospitals, and in 1996 developed a catatonia rating scale and an effective systematic treatment algorithm.

Another venue, other questions. In 1966 I assumed responsibility for a New York City opiate detoxification center treating opiate dependence by narcotic antagonists, either naloxone or cyclazocine or the longer acting opioids of methadone and levomethadyl. An opportunity to study hashish users in Athens showed that chronic use of high potency cannabis does develop tolerance and dependence, but the level of toxicity was not that of opioids or cocaine and did not warrant the restricted classification assigned by the Federal government, a finding that is consistent with the ongoing national state-by-state legalization of cannabis sale and use. We also showed that the principal active component was THC-Δ-9 and that its concentration is a useful marker of potency of samples, much like percent alcohol is a measure of alcoholic beverages.

Not all efforts survived the passage of time and science. My 35-year effort to classify psychiatric medications by their quantitative EEG patterns using digital computer programs became the core of the science of pharmaco-EEG. We identified active agents and their role in selected illnesses and labeled other agents as ineffective placebos. But the professions lost interest and the science is no longer actively pursued. The likelihood that the science will be revived is slim, considering the little interest in brain electrophysiology by clinicians outside of epilepsy.

I developed an interest in the clinical syndrome of melancholia, with enthusiasm for the dexamethsone suppression test as a measure of the role of the adrenal glands in this toxic state (which is eminently responsive to ECT). Competing interests and lack of research support left me with publishing a *Melancholia* textbook with Michael Taylor in 2006 but I made no contributions to this science. A few years later I tried again to stimulate interest by publishing a detailed history of the syndrome with the historian Edward Shorter.[2] These efforts failed to influence the professions, although I was always delighted to identify melancholia or its variants in delusional or psychotic depression, or post-partum psychosis, because such patients were eminently responsive to electroshock.

Consent: A swinging pendulum.

The massive chemical and air warfare of the World Wars calloused societies to death. Lives mattered little as massive air bombings shattered civilian populations, as nations selected innocent populations by religion or color to be killed. Medical practice became hardened as the mentally ill and the retarded were selectively murdered to "purify the gene pool." In my medical school and residency training I treated patients without explanation or their signed consent, beyond the single global acceptance of in-hospital admission for treatments to be decided by the institution staff.

The deadened sensitivity to patient welfare allowed fever therapy by infecting syphilitic patients with malaria – a procedure that was heralded by the Nobel Prize. That insensitivity encouraged the comas of insulin, the epileptic seizures of Metrazole and electricity, and the surgical brain cutting of lobotomy, another procedure enthusiastically endorsed by yet another Nobel Prize. These assaults were widely accepted and in modified form remain part of present day psychiatric practice.

That is how maggots were tested in children with osteomyelitis; trypan red infusions were adminsitered to those with amyotrophic lateral sclerosis; and an "unknown" substance (penicillin) used alternately to wash out the pus of empyema. The CSF of patients with syphilis was obtained by a cisternal puncture carried out by a neophyte medical student, a procedure now considered so riskful as to be interdicted.

It was as a resident trainee that I carried out the new procedure of percutaneous carotid angiography in 102 patients with a 5% morbidity rate. When chlorpromazine was a newly

introduced agent before we knew of its risks, I selected half the patients assigned to insulin coma for a test of its merits. When a new anesthetic flurothyl was shown to induce seizures, I treated dozens of patients referred for electroshock. And when a new muscle relaxant, succinylcholine, was introduced for electroshock, I tested its use in a succession of patients without asking for specific consent.

The first hint of patient consent for clinical treatment and research came in the mid-1960s with the NIH suggestion that an independent lay and professional body known as Institutional Review Board to review whether research protocols met highest safety and ethical standards. Slowly, the Boards asked for individual consent to participate, and increasingly they restricted studies. So much so, that today every clinical research study has to overcome high hurdles in individual consent, investigators have to meet institutional certifications for human research by training courses and individual testing and certification.

As the MIP director in St Louis in 1965 I organized an independent IRB under the aegis of the Psychiatric Research Foundation of Missouri with lay, legal, and science representation. I did the same in New York when research projects were supported by the International Association for Psychiatric Research, a lay membership board that reviewed all my projects.

Individual signed consent for ECT became an issue for the members of the American Psychiatric Association Task Force on ECT that recommended individual consent for the course of treatments in its 1978 report. I was uncomfortable in accepting such a restriction of my practice but did agree and have insisted on such individual consent in all my treatments. In my extensive pharmaco-EEG studies undertaken after the 1960s, especially in our volunteers, we developed detailed subject consents for each study.

My studies were undertaken during a special period of human research that enabled me to do many procedures that are not feasible today. The losses to our learning are severe, and the impediments high for modern clinician researchers. Sadly, these skills that taught us much are now severely inhibited, driving more and more studies to animal trials (even these have special hurdles) and laboratory procedures by non-physicians. Much knowledge is being lost.

The State of Psychiatry in the 21st Century

The long, unfortunate association of catatonia with schizophrenia was worsened by psychiatry's continuing rejection of the physical examination and its reliance on verbal inquiries

and on visual observation of behaviors for practical diagnosis. Catatonia signs are best observed as responses to simple commands, but they do require "hands-on" examination. The patient is asked to respond to simple commands. For most psychiatric illnesses, the labels and the explanations are commonly based on ephemeral concepts of mind, with neglect of the role of brain and systemic functions even if the prescription ends up being a chemical pill. Diagnosis is based on interview questions, most often directed to family members and other observers. Sadly, the enthusiastic following of Sigmund Freud's rich imagination and prolific writings divorced the discipline from clinical medicine.[3]

Psychiatric practice today depends on two skills – knowledge of medications that alter brain functions and verbal "psychotherapies" deemed but unproven to be therapeutic. Verbal therapies do not relieve the severe psychiatric ill, those with psychosis, depression, mania, anxiety, or catatonia. They are directed to the "walking wounded," the sad unhappy citizens whose social expectations are not being met. Government approval for marketing medications is assured when patient records show a 50% reduction in rating scale item scores in two studies in comparisons of a new compound and a similar marketed compound, only occasionally compared to a chemically inactive (placebo) medication. But, the efficacy of psychoactive medications depends on the changes that they induce in brain functions readily evidenced by the patient's EEG patterns. Failure to induce EEG changes is associated with minimal to no effects beyond that of a placebo. Todays' marketed pills affect the EEG minimally; neither the SSRI and SNRI antidepressants, the atypical antipsychotics, or the anticonvulsants touted for mania have demonstrated EEG effects and clinical benefits. They are no better than sugar pills.

The recording of brain waves was introduced in 1929 and for a few decades was a skill sought by neuropsychiatrists, I among them. In the past half century, however, the EEG has come to be used mainly by neurologists to monitor seizure disorders. Psychiatrists and pharmacologists express little or no interest in EEG patterns, having relinquished the discipline to the epileptologists. Even when EEG information is recorded, as it is in modern ECT devices, its messages are ignored, even though an examination of the seizure characteristics distinguishes effective and ineffective treatments. Except for the single criterion of length of the recorded seizure, no aspect of the seizure isexamined and recorded. The interseizure EEG that I found useful in identifying a successful course of treatment is ignored. This failure to use an effective criterion of each treatment and the course of treatments leads to poor and missed seizures and the

under-treatment of patients with high relapse rates.

Psychoactive drugs do alter the EEG, even if minimally, and do offer criteria for effective dosing. Agents that are clinically antidepressant, antipsychotic, anxiolytic, hallucinogenic, and deliriant elicit characteristic changes in quantitative EEG recordings that predict clinical effects, identify effective dosage ranges, and distinguish active from placebo agents.[4] But such knowledge is ignored in today's psychiatric practice and research.

Some few treatments, mainly lithium therapy, are monitored by serum blood levels. For a short time, serum levels of nortriptyline showed that many patients were undertreated, but the use of the tricyclic drugs is no longer active. Monitoring of body fluids and physiologic effects induced by prescribed drugs is eschewed, leaving psychiatric practice at the level of Shakespeare's witches.

Identifying catatonia populations by defined characteristics – acute onset of illness, measurable motor behaviors, test relief by barbiturates and benzodiazepines, and relief with induced seizures -- is an opportunity to identify and study more homogeneous psychiatric patient samples for neuroscience studies. Alas, neuroscientists seek to understand psychiatric illnesses by brain imaging and genetic profiling of clusters of patients defined by imprecise DSM characteristics. Heterogeneity is assured and that does not bode well for the search for genetic markers or characteristic brain images.

In Retrospect

As I recollect this history, some chapters are painful to recall, entailing episodes that cast long shadows of professional conflicts and failures. That was most true about my time in Missouri – unfulfilled expectations, little learned, and little that made me happy. But the chapter of my working life marked by the awakening to catatonia, the success in identifying patients with the illness, and the pleasure that came as patients recover and return to their homes, is most satisfying. The divorce now of catatonia from schizophrenia in psychiatry's DSM is gratifying indeed, offering many ill the promise of recognition of the illness and the relief by effective treatments. My teachers should feel rewarded as should my students. Was it for this story that I defended electroshock and kept it alive as an ongoing treatment despite the criticisms of professional colleagues? A most rewarding aspect was the seredipitous publication of Heckers' report endorsing my view of catatonia on my 92nd birthday in 2015! My e-mails continue with notes from Lee Wachtel and Barry Kramer reporting the story of an adolescent Shane, diagnosed with self-injurious behaviors in autism who is able to remain in the community so long has he gets weekly treatments. The relief is rewarding but sadly, the relief is that akin to insulin in diabetes not to that of penicillin in neurosyphilis. We've made some progress, but we have long ways still to go.

In Gratitude

My debts to my parents, my wife Martha, my teachers, my students and my patients aremany, acknowledged throughout this story in the text and footnotes. My parents encouraged me to follow in their footsteps and I was fortunate to be admitted to medical school when admissions were severely restricted to members of my faith. My teachers in medical school and residencies encouraged research studies as a primary responsibilty of the physician. I entered medicine during a time of increasing public funding of studies in humans, and my studies were well supported by my family and by friends Arnold and Phyllis Canter, Maria and Henry Feiwel, Martin and Alice Green, Blanche and Melvin Muroff, and Donald and June Shapiro who established the non-profit International Association for Psychiatric Research.

The list of teachers and colleagues is long, each often cited in this story. I owe much to Morris B. Bender, Edwin Weinstein, Bernhard Dattner, William Karliner, Alfred Freedman, George Ulett, Lothar Kalinowsky, Stanley Yolles, and Fritz Henn for their teaching,

encouragement, and support of my studies. I learned much from my colleagues and collaborators Jan-Otto Ottosson, Max Hamilton, Jonathan O. Cole, Tom Bolwig, Robert L. Kahn, Donald F. Klein, John C. Kramer, Donald M. Shapiro, Richard Abrams, Michael A. Taylor, Turan M. Itil, Samuel Gershon, Jan Volavka, Rhea Dornbush, Richard Resnick, Arthur Zaks, Peter M. Irwin, Yiannis Papakostas, Ioannis Zervas, Dirk Dhossche, George Bush, Andrew Francis, Charles Kellner, Teresa Rummans, John Rush, Irene Carasiti, Samuel Bailine, and Georgios Petrides.

The historians Edward Shorter and David Healy undertook the writing of a history of the shock therapies, visited my home, and encouraged me to deposit my archives at the Stony Brook University Library. They fathered the writing of this life story. Writing has been well assisted by Kristen Nyitray, SBU archivist.

My textbook and the editing of the journal *Convulsive Therapy* was supported by the publisher Alan Edelson. Numerous editors including Richard Marley of Cambridge, George Zimmar of Routledge, Sarah Harrington and Craig Panner of Oxford were encouraging. And the editor Jonathan Cobb edited these pages with patience and skill.

I owe much to the support of my children Jonathan, Rachel and Linda who have actively supported me since my wife Martha died in March 2016, after 67 years of a loyal, loving and happy marriage. These writings are dedicated to her, for none of the work would have been accomplished except for her encouragement and support.

Notes and References

Epigraph

[1] Arthur Wallace:. *Creatures of Accident*. New York: Hill and Wang, 2006.

01 Starting Out

[1]We lived a happy 57 years together until Martha died of a sudden cerebral stroke on March 31, 2016. We planted a Japanese Cherry tree in memorium at our home in Nissequogue. It was moved to Rachel's home in South Hadley on March 27, 2018.

[2] My initial annual Hillside Hospital salary in 1953 was $12,500, the same sum that was paid for each acre of Hillside Hospital land to establish the newly formed Long Island Jewish Hospital. The "baby" grew and soon incorporated the psychiatric hospital and then a nearby North Shore Hospital in Manhasset, one hospital after another on Long Island, then Staten Island until, at this writing at the end of 2016, it is a conglomerate of 18 hospitals, research centers, rehabilitation and skilled nursing facilities, a home care network,a hospice network, and progressive care centers[1] offering a range of outpatient services.

On March 22, 2017 I visited the medical center to attend a lecture by Edward Shorter of Toronto and was amazed at the megalopolis that was now the medical center. The "cottages" were replaced by a new clinical facility with a robust ECT treatment center with 3 treatment rooms, multiple recovery rooms, and offering from 25 to 35 treatments each day to inpatients and outpatients.

[3] Academic salaries were quite adequate for my family, supplemented after my return to New York in 1966 by a salary from the International Association for Psychiatric Research that I organized to support cannabis research studies under an NIH contract. Occasional consultation fees from industry to participate in clinical drug trials, and consultations as an expert witness in legal malpractice cases, mainly in defense of ECT and the use of various psychotropic drugs, supplemented my academic salary. In addition, I was often paid nominal fees at academic centers for grand round lectures in the U.S. and Europe.

[4] The model support center was established earlier in St. Louis as the Psychiatric Research Foundation of Missouri as a non-profit educational institution under Section 501(c)(3) of the Internal Revenue Code. The foundation used grant funds but also applied grant overhead funds for personnel, equipment and travel costs. The IAPR managed grants for studies at Stony Brook University, particularly those associated with the digital computer laboratory. After 1985, when the IBM laboratory equipment was sold, the foundation changed its goals and Board membership to support college-level studies in the sciences. The name was changed to the Scion Natural Sciences Association.

[5] That night in SFO I suffered a kidney stone, called for medical help, was taken to SFO General Hospital. I presented my report at the meetings Monday afternoon and then flew home that night for medical care in Great Neck with Dr. Norman Rosenthal. The stone passed and I did not have another episode. In retrospect, the mishap was encouraged by dehydration and the stress of flying. Denber returned home alone.

[6]. Jonathon married Dr. Nina DeLange and has two children, Laurel who graduated from Arizona State University and completed a Master's degree in environmental studies at the University of Brisbane, Australia in 2016, and Andrew who is a junior at the University of British Columbia. Rachel married Dr. Tom Dennis, an astronomer and they adopted two children, Rose Dennis now a graduate of Mount Holyoke College and Hieu Jacob Dennis, a junior at Union College in Schenectady, New York. Linda married Lincoln Brower, an international expert in the study of the Monarch butterflies. They live in a 360 acre retreat in the Blue Ridge Mountains near Jefferson's Monticello.

[7]Each mastered their academics and went on to graduate degrees, Jonathan in geology at Stanford, Rachel in cell biology at Duke, and Linda in environmental studies and entomology at University of Florida in Gainesville. They

went on to academic careers, Jonathan at Arizona State University and then Portland State University. Rachel at Mount Holyoke College, and Linda at Sweet Briar College.

[8] The Finding Aid to the collection describes the collection:
Repository: Special Collections and University Archives, University Libraries. Stony Brook University Libraries (State University of New York) Frank Melville, Jr. Memorial Library, Room E-2320 http://library.stonybrook.edu Stony Brook, NY 11794-3323; 631.632.7119 (t); 631.632.1829 (f)
Creator: Max Fink, M.D. (1923-)
Provenance: Gift of Max Fink to the Stony Brook Foundation; received in a series of accessions between 2006 and 2015.
Dates: 1880s-2015 (1950-1990, bulk) Extent: 243 linear feet (464 boxes; five map file drawers)
Languages: English, German, French, Greek, Spanish, Hungarian, and Russian.

02 Schooling

[1] Drs. Carl Sandstrom and Horace W. Stunkard were the leading professors of biology.

[2] During my first year at Bellevue Hospital I was inducted into the Army as PFC in the 3224 Service Command Service Unit, serial # 01716837MC. With my medical school graduation on June 12, 1945 I was appointed Lieutenant First Class in the Army Medical Corps. After 9-months temporary duty as a medical intern at the Morrisania City Hospital in the Bronx my active military service began in April 1946 at the Brooke Army Center for basic medical training, then neuropsychiatry training 17 Feb 47 to 6 June 47 at the School for Military Neuropsychiatry at Fort Sam Houston, certified specialist 3130C and promoted to Captain. Before NP School I was with the 2nd Infantry Regiment, Fifth Infantry Division at Camp Campbell, KY; after NP School I was in charge of the Psychiatry wards at Ft Knox Station Hospital, KY. I was Honorably Discharged from military service December 4, 1947.

[3] Schönbauer L, Jantsch M. *Julius Wagner-Jauregg Lebenserrinerungen*. Vienna: Springer-Verlag, 1950.

[4] Dattner had developed his skills in the clinic of Julius Wagner-Jauregg.
Dattner B. *Moderne Therapie der Neurosyphilis*. Vienna: Maudrich, 1933.
Dattner B. *Moderne Therapie der Neurosyphilis: mit Einschluss der Funktionstechnik und Liquoruntersuchung*. Vienna: Verlag Wilhelm Muadrich, 1933.
Dattner B, Thomas EW, Wexler G. *The Management of Neurosyphilis*. NY: Grune & Stratton, 1944.

[5] Before this rotation in my training I had learned the technique of lumbar puncture for CSF during a month on the anesthesia service. Cisternal puncture, the insertion of a needle through the nape of the neck to obtain CSF, seemed a modification of the lumbar puncture method to obtain cerebrospinal fluid. Cisternal puncture was a technique believed to reduce post-spinal headache.. It was not until I returned to my neurology residency a few years later that my attending physicians in neurology did not permit the procedure as too riskful, insisting that only lumbar samples were acceptable.

[6] The lesson that using a guide to severity and progress in treatment was well learned and applied throughout my research career, first in applying the amobarbital test of organic mental syndrome, the Face-Hand test for mental age, the quantitative EEG to monitor psychoactive drug trials, to the lorazepam relief test as a verification of the catatonia diagnosis and progress in treatment.

[7] Fever therapy is resurrected from time to time in dread diseases. At the height of the AIDS epidemic, a trial was tested. More recently, a single episode of fever induced in a sweat box was reported as reducing the depression rating scale scores of a patient with major dedpressive disorder. The report, published in the most prestigious psychiatry journal, led me to write to the editor (Stefan Heckers) indicating that while a proper Random Controlled Trial the findings had no clinical significance.
Janssen CW et al: Whole-Body hyperthermia for the treatment of major depressive disorder: A randomized clinical trial. *JAMA Psychiatry*. 2016 73(8):789-95.

Fink M, Shorter E. Hyperthermia for Major Depressive Disorder? *JAMA Psychiatry*. 2016 Oct 1;73(10):1096. doi: 10.1001/jamapsychiatry. 2016.1627.

[8] By the 1970s, such experiences were no longer accepted by the students. In 1975, at the newly established medical school at Stony Brook, Long Island, my suggestion that students experience the effects of medications under supervision was not approved by the Dean. The school was in the throes of puzzlement on how to deal with the pervasive campus use of illicit drugs.

[9] Maggot therapy is actively used in military wounds. See Roach, Mary. *Grunt: The Curious Science of Humans at War*. NY: Norton, 20l6.

[10] Amobarbital for the relief of catatonia was introduced in 1930 by Bleckwenn in a report and a remarkable film, available from the National Library of Medicine. It was the first sign of the forthcoming psychopharmacology era. I did not realize this significance until I studied the history of catatonia decades later. (Fink and Taylor, 2003).

[11] The temperature charts that I produced are published in Rubin EH. *Diseases of the Chest With Emphasis on X-ray Diagnosis.* Philadelphia PA: WB Saunders Co., 1947. My work was nicely acknowledged but the lesson of the importance of adhering to patient selection in random controlled trials was learned.

[12] Alas, on leaving school I was one of two students who did not receive a "Good Conduct" Army medal.

[13] 2nd Infantry Regiment, Fifth Infantry Division, then at Camp Campbell, Kentucky.

[14] I, also, was sufficiently intrigued to undertake psychoanalytic training, made feasible by the government's program of student aid (the GI Bill) to honorably discharged military personnel. Psychoanalytic training in New York City was offered by the New York Psychoanalytic Institute, Columbia University, and Downstate Medical Center in day-time classes, with students learning from patients in their clinics. Such a schedule precluded a normal hospital residency. One school, the William A. White Institute offered evening and Saturday courses. I attended classes for five years, concurrent with my residency training at Bellevue and Hillside Hospitals. My teachers included David Rioch, Janet MacKenzie Rioch, Edwin Weinstein, Frieda Fromm-Reichmann, Clara Thompson, and Ralph Crowley. My personal analyst was Joseph Miller of the Institute faculty. I graduated with their Certificate for Physicians in 1953.

[15] Arthur Benton went on to head the Psychology Department at the University of Iowa. He developed the Benton Visual Retention Test within a battery of psychological tests. The Rorschach test -- the subject's responses to 10 "inkblot" cards -- offered quantitative scores as to number of responses (N), their basis in the whole image or parts of the image (W, P), whether the images were reorted as moving (M), whether based on Form (F), and others. I used the Rorschach Test responses in my studies of convulsive therapy and psychoactive drugs. These are summarized in the 1979 text *Convulsive Therapy: Theory and Practice.*

[16] In the Korean War, Congress recalled Medical officers from the Reserves who had served less than 21 months of active duty. I was recalled to active duty. A question was raised whether the "21 month" cutoff was constitutionally proper and my orders were temporarily suspended. In time, the Courts decided that the 21 month cutoff was arbitrary and my orders to active duty were rescinded.

[17] I left New York on December 12, 1947 and spent New Year's Day swimming in the Pacific off the coast of Vina del Mar (Valparaiso). A second trip with a similar route followed. My next trip was on the *S.S. Santa Monica* to Cartajena and Barranquilla from March 24 to April 14. My final trip was with the American Export Lines' *S.S. Marine Perch*, a troop carrier to Palermo and Naples (with a 36 hour trip to Rome).

[18] In Buenaventura, Colombia I visited a local hospital managed by nuns and observed the delivery of an infant on an oilcloth covered table. The Hospital was equipped with a modern surgical suite, a gift of the Rockefeller Foundation. Surgeons came once weekly from Bogota.

[19] In a visit to Lima, Peru I met Honario Delgado. He encouraged his patients to express their thoughts and moods in paintings, drawings, and sculptures, art that covered the walls and floors of the otherwise grim asylum. He anticipated the world enthusiasm for "Outsider Art" by two score years.

[21] It was on this trip that I first met Bertie and Harry Gross. When the ship returned to New York their daughter Martha Pearl Gross, a student at Barnard College in New York City, met the ship. Subsequently we courted and married on September 11 a year later.

[22] Kenneth Gang, Stanley Stellar, Joseph Ransohoff, and Harvey Gass were neurosurgical residents. The chief neurosurgeon was Leo Davidoff.

[23] At the Missouri Institute we examined the electroencephalogram (EEG) and the pneumoencephalogram (PEG) of patients who had been lobotomized some years earlier and were still resident at the St Louis State Hospital. We found no significant abnormalities; the images of the frontal lobes were intact. I was in the PEG laboratory with a needle in a patient's back as the hospital operator announced that President Kennedy had been killed. Later, at Stony Brook I obtained the CSF for neuroendocrine studies of patients during the course of ECT.
Nemeroff CB, Bissette G, Akil H. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry* 1991; 158: 59-63.

[24] Joseph Stein was born January 27, 1924; graduated Columbia College and NYU College of Medicine in 1947. After training he moved to Topeka, KS joining the faculty of the Menninger Foundation. He died July 24, 2013.

[25] Fink M, Stein JM. A clinical evaluation of carotid angiography. A review of 117 patients. *Confin Neurol* 1952; 12:181-95. While the diagnostic reliability for aneurysms and brain masses was high, so was the complication rate with two deaths within 24 hours and five patients suffering hemiparesis.

[26] Fink M, Stein JM. Spinal fluid findings following cerebral angiography. *Neurology* 1953; 3:137. No changes in CSF were found.

[27] Fink M. Denial of blindness following cerebral angiography. *J Hillside Hosp* 1956; 5:238-245.

[28] Weinstein EA, Linn L, Kahn RL. Psychosis during electroshock therapy: Its relation to the theory of shock therapy. *Am J Psychiatry* 1952; 109:22-26. When I developed a research program to understand the mechanism of ECT, one interest was to test the denial hypothesis.
Fink M. A unified theory of the action of physiodynamic therapies. *J. Hillside Hosp.*, 1957; 6: 197-206.

[29] Morris Bender (1905-1983) was born in Russia, graduated University of Pennsylvania in 1930. Began an association with the Mount Sinai Hospital in 1933. During World War II on military service he discovered visual extinction on simultaneous stimulation. After the war he taught first at NYU and then chaired a strong Department of Neurology at Mount Sinai Hospital. He summarized his sensory studies in *Disorders in Perception* (C. C Thomas, 1952). A Festshrift in his honor was edited by EA Weinstein: *Journal of the Mount Sinai Hospital* 1974; 41(1): 1-248. Also Cohen B: Morris B. Bender 1905-1983. Obituary. *Neurology* 1983; 33:1335-1336.

[30] Edwin A. Weinstein (1909-1998) combined training in neurology and psychoanalysis. He published *Denial of Illness* with Robert L. Kahn in 1955 (C.C Thomas, Springfield IL). He developed a concept that the psychological defense of denial was central to the improvement shown of depressed patients treated with induced seizures and applied this concept in a biography of President Woodrow Wilson (Weinstein EA: *Woodrow Wilson: A Medical and Psychological Biography*. Princeton NJ: Princeton University Press, 1981.)

[31] Fink M, Green M, Bender MB. Patterns in perception of simultaneous tests of face and hand. *Arch. Neurol. Psychiat.* 1951:66: 355-362;
Fink M, Green M, Bender MB The face-hand test as a diagnostic sign of organic mental syndrome. *Neurology* 1952: 2: 46-58.

Fink M, Bender MB. Tactile perceptual tests in the differential diagnosis of psychiatric disorders. *J. Hillside Hosp.*, 1952; 1*:* 21-3.
Shapiro MF, Fink M, Bender MB. Exosomesthesia, or displacement of cutaneous sensation into extra-personal space. *Arch. Neurol. Psychiat.* 1952; 68: 481-490.
Fink M, Green M, Bender MB. Patterns of perceptual organization with simultaneous stimuli. *Arch. Neurol. Psychiat 1954:* 72: 233-255.
Fink M, Bender MB. Perception of simultaneous tactile stimuli in normal children. *Neurology 1953;* 3: 27-34 9.
Fink M, Green M, Bender MB. Perception of simultaneous tactile stimuli by mentally defective subjects. *J. Nerv. Ment. Dis.*, 1953; 117: 43-49.

[32] Fink M, Kahn RL, Weinstein EA. The "Amytal Test" in patients with mental illness. *J Hillside Hosp* 1955; 4: 3-13.

[33] Korin H, Fink M. Role of stimulus intensity in perception of simultaneous cutaneous electrical stimuli. *J Hillside Hosp* 1957; 6:241-50;
Pollack M, Fink M. Disordered perception of simultaneous stimulation of face and hand: Review and Theory. In: J. Wortis (Ed.): *Biological Psychiatry*. NY: Plenum Press, 1962; 4:362-69.

[34] Tarachow S, Fink M. A statistical study of a psychoanalytic hypothesis: absence of a parent as a specific factor determining choice of neurosis. *J. Hillside Hosp.*, 2: 67-71

[35] Fink M. Homosexuality with panic and paranoid state. *Journal of Hillside Hospital* 1953; 2: 164-190.

[36] A better example of how antipathy to homosexuality destroyed a valuable life is the life of the British mathematician Alan Turing who was instrumental in solving the German codes during WW II. Turing, the father of modern computers, was convicted of gross indecency and offered prison or chemical castration. He suicided at age 42. Hodges A: *Alan Turing: The Enigma*. Princeton NJ: Princeton University Press, 1983.

[37] Berger H. Uber das elektroenkephalogram des Menschen. *Arch Psychiat NervKrankh* 1929; 87: 527-570.

[38] Recordings were obtained from the exposed animal and human brain beginning in 1875.

[39] I shared the office in Great Neck with Walter Glass, a specialist in Ear, Nose & Throat illnesses, at 275 Middle Neck Road. I developed an active practice in neurology consultations, psychotherapy, and modified ECT administered in the office.

[40] Hans Strauss was trained in neurology in Germany, emigrated to New York in 1937, and established one of the first EEG Laboratories in the US. He was a specialist in epilepsy. Strauss H, Ostow M, Greenstein L. *Diagnostic Electroencephalography*. New York: Grune & Stratton, 1952.

[41] Mortimer Ostow began with an interest in EEG. He was a member of the *Group Without A Name*, a society of analysts and biological researchers. His primary interests, however, were in psychoanalysis.

[42] NIMH M-927, awarded in the summer of 1954.

[43] In 1954 I established the Department of Experimental Psychiatry with Robrt L. Kahn, Ph.D., Hyman Korin, Ph.D., Eric Karp, M.A., Martin a. Green, M.D. and George Krauthamer Ph.D., as research associates; Hanna Mosquera as EEG technician supported by NIMH 927. Other grants from NIMH (MY-2092, MY-2715), the Foundations Fund for Research in Psychiatry, the Mental Health Board of Nassau County, and various pharmaceutical firms supported Max Pollack, Ph.D, Joseph Jaffe, M.D., Donald F Klein, M.D., and Nathaniel Siegel, Ph.D.

[44] My initial annual Hillside Hospital salary was $12,500, the same sum that was paid for each acre of Hillside Hospital land to establish the the newly formed Long Island Jewish Hospital. That entity grew and soon incorporated the psychiatric hospital and then a nearby North Shore Hospital in Manhasset, one hospital after

another on Long Island, then a unit on Staten Island until, at this writing at the end of 2016, it is a conglomerate of 18 hospitals, research centers, rehabilitation and skilled nursing facilities, a home care network,a hospice network, and progressive care centers[L] offering a range of outpatient services.

[45] Academic salaries were very adequate for my family, supplemented after my return to New York in 1966 by a salary from the International Association for Psychiatric Research that I organized to support research studies under an NIH contract for the Greek cannabis studies. Occasional consultation fees from industry to organize clinical drug trials, and consultations as an expert witness in legal malpractice cases, mainly in defense of ECT and various psychotropic drugs, supplemented my academic salary. And I was often paid nominal fees at academic centers for grand round lectures in the U.S. and Europe.

[46] Although a few state hospital units had established research units affiliated with university centers before WW II, such units were established post-war throughout the nation, encouraged by the Federal government's National Institute of Mental Health.

[47] Individual case reports are described in Fink M. *Electroshock: Restoring the Mind*. New York: Oxford University Press, 1999 and in the second edition titled *Electroconvulsive Therapy: A Guide for Professionals & Their Patients*, 2009.

[48] The most common image of ECT is that of Jack Nicholson in *One Flew Over the Cuckoo's Nest* of 1975.

[49] Fink M. Optimizing ECT. *L'Encephale* 1994; 20: 297-302;
Fink M. *Electroshock: Restoring the Mind.* NY: Oxford University Press, 1999.

[50] Fink M. What was learned: studies by the consortium for research in ECT 1997-2011. *Acta Psychiatr Scand* 2014; 129:417-426.

03 Inducing Seizures: Hillside 1952-1962

[1] Simon Kwalwasser received his medical training at St Andrews University, trained in psychoanalysis, served as Associate Medical Director at Hillside. Supervised psychotherapy treatment. He encouraged the studies in ECT with an interest in the changes in memory.

[2] Fink M. *A Beautiful Mind* and insulin coma: social constraints on psychiatric diagnosis and treatment. *Harvard Review of Psychiatry* 2003; 11: 284-290.

[3] Rachlin HL, Goldman GS, Gurvitz M, Lurie A, Rachlin L. Follow-up study of 317 patients discharged from Hillside Hospital in 1950. *J Hillside Hospital* 1956; 5:17-40.

[4] Gordon HL. Fifty shock therapy theories. *Milit Surg* 1948; 103:397-401.

[5] Gloor P. (Ed.) Hans Berger and the electroencephalogram of man. *Electroenceph clin Neurophysiol*, Supplement 28, 1969, 350pp.

[6]In 1964, I published a list of 580 references from my personal collection of articles that described the effects of drugs on the human EEG. Fink M. A Selected Bibliography of Electroencephalography in Human Psychopharmacology 1951-1962.*Electroenceph Clin Neurophysiol* 1964; 16: Suppl 23.

[7] Bradley P, Fink M. (Eds): *Anticholinergic Drugs and Brain Functions in Animals and Man. Progress in Brain Research*, Vol.28, Elsevier, Amsterdam, pp. 375, 1965.

[8] Fink M. Experimental psychiatric research at Hillside: review and prospect. *J. Hillside Hosp.*, 1961: 10*:* 159-169.

[9] John C. Kramer completed his residency training and a USPHS Research fellowship at Hillside with emphasis on clinical evaluation of new drugs. His report on withdrawal symptoms after imipramine was often quoted. He left for New Mexico and Los Angeles studying intravenous amphetamine and opioid abuse. He was consultant to Jerome Jaffe at SAODAP. His father was an MD practitioner in the Bronx, a colleague of my father.

[10] After I left Hillside in 1962, Donald Klein headed the research program. He had joined me in 1955. He was less interested in neuropsychology, ECT and EEG and soon each of my colleagues left for other careers. Klein left for a position at Columbia University with Edward Sachar. The research program was next led by John Kane, whose emphasis was on the motor aspects of antipsychotic drugs, focused on clozapine and risperidone. He headed the Hillside Hospital when it became a stepchild of the much larger Long Island Jewish Hospital. He was replaced by Jeffrey Liebherman whosed interest was in brain imaging and psychotropic drugs. He left to chair the Columbia University Psychiatry Department.

[11] Martin Green, M.D. graduated the University of Michigan 1945 and joined the neurology residency programs at Bellevue, working under Morris Bender. We collaborated in the Face-Hand studies. He opened a medical practice, managing the EEG services at Long Island Jewish and North Shore Hospitals. In March 1954 he joined the Experimental Psychiatry group managing EEG and ECT studies. He was a supporter of the International Association for Psychiatric Research Board. His wife Alice and 3 children, Andrew, Shannah, Deborah were life-long friends.

[12] Joseph Jaffe, M.D. graduated NYU in 1947 and took his further training at Bellevue and also graduated the William Alanson White Psychoanalytic training program. He became interested in psycholinguistics assessing changes in language measures like the Type-Token Ratio in ECT and psychoactive drugs.

[13] Robert L. Kahn graduated Brooklyn College in 1940, received his Ph.D. at NYU in 1953, worked at Mt Sinai Hospital with Edwin Weinstein. Their study *Denial of Illness* was the classic basis for the early studies of ECT. He joined the Hillside staff in January 1954. His skills in psychological testing and statistics was a central moving force of our experimental research studies.

[14] Max Pollack received his Ph.D. at New York Univeristy in 1955 and joined the Hillside staff in November 1954. He was instrumental in studying the impact of social class and aging on psychological tests, effects of psychoactive drugs.

[15] Nathaniel Siegel, Ph.D., a sociologist, joined the study group to work with Max Pollack on social class and aging issues in ECT and psychoactive drug studies.

[16] Hyman Korin received his Ph.D. at NYU in 1952, joining the Hillside research group in 1953. He undertook quantitative studies of the Face-Hand Test and of memory in relation to ECT and psychoactive drugs.

[17] Fink M, Kahn RL, Weinstein EA. The "Amytal test" in patients with mental illness. *J. Hillside Hosp.*,1955; 4*:* 3-13;

Fink M, Kahn RL, Weinstein EA. Relation of Amobarbital test to clinical improvement in electroshock. *Arch. Neurol. Psychiat. (Chic.)*, 1956; 76: 23-29.

[18] An organic mental syndrome (OMS) or organic brain dysfunction was the description applied to the disorientation, confabulation, confusion, and poor recall that occurs in patients with gross brain dysfunction following trauma, stroke, and drug overdoses. In such patients the FHT is positive, performance on coghnitive tests is poor, denial responses prominent. Immediately after a seizure, these signs are present accompanied by slowing of the EEG.

[19] Fink M, Kahn RL. Behavioral patterns in convulsive therapy. *Arch. Gen. Psychiat.*, 1961;5*:* 30-36;
Klein DF, Fink M. Psychiatric reaction patterns to Imipramine (Tofranil). *Amer. J. Psychiat.*, 1962;119: 432-438;
Klein DF, Fink M. Behavioral reaction patterns with phenothiazines. *Arch Gen Psychiatry* 1962; 7:449-459.

[20] Fink M. A unified theory of the action of physiodynamic therapies. *J Hillside Hosp* 1957; 6:197-206. This view was restated and amplified in: Fink M. The mode of action of convulsive therapy: the neurophysiologic-adaptive view. *J. Neuropsychiat.*, 1962; 3: 231-233.

[21] The teaching of Drs. Morris Bender, Edwin Weinstein, Nathan Savitsky, and Bernhard Dattner were especially encouraging.

[22]The 1950s were a decade before the restrictions on human studies that befell medical research after the forced draft of citizens during the Vietnam War, protests over lack of patient consent, and public outcries against arbitrary government actions that dominated the nation thereafter. The freedom to design and undertake studies was central to research related to medical care at academic centers before the awakening of ethical questions. I was unaware then of the privileges that permitted my studies, but as I describe these experiences in the face of modern restrictions I am increasingly aware that my research career was much favored by the times.

[23] Fink M. *Convulsive Therapy: Theory and Practice*. New York: Raven Press, 1979.

[24] During a lecture tour to five cities in India in 2001, I was questioned about my experience with unmodified ECT and my view of the ethics of its use. I took the position that for the severe mentally ill unmodified ECT was surely to be preferred to no ECT. The debates were active, and by 2013 India's national legislature had restricted the use of unmodified ECT.

[25] In the pre-psychoactive drug age, these records were considered "normal" for the subject's age. Such measurements became difficult in the decades after psychoactive drugs became the common treatment of psychiatric patients coming to the EEG laboratory. With patients having been pre-treated with a plethora of psychoactive drugs over varying times, studies of changes from baseline recordings became increasingly difficult.
An excellent portrayal of the "normal EEG" varying with age is published by Milos Matousek, Jan Volavka and Jiri Roubicek in *Cesk Psychiatr* 1967; 63(2): 73-8; and *Cesk Psychiatr*. 1967; 63(1):14-9. All three left Prague in 1968 with the invasion by Russia. Roubicek and Volavka emigrated to the USA joining my Department at the New York Medical College to study the EEG effects of ECT, opioids, and cannabis. Matousek emigrated to Sweden.

[26] The technology of ECT devices improved with better control of energies; by 1978 I had a MECTA device built by Paul Blachly of Portland OR that recorded the EEG seizure. By that time I had developed digital computer programs to digitize the EEG signal and provide quantitative measures using period analysis and power spectrum programs. These programs were adapted for the THYMATRON ECT device built by John Pavel, the engineer in my research team at the New York Medical College, for the Somatics Corporation organized by Conrad Swartz and Richard Abrams in early 1980s. The audible EEG, developed by John and Nick Pavel at my suggestion, was also incorporated in THYMATRON devices.

[27] Fink M. The seizure, not electricity, is essential in convulsive therapy: The flurothyl experience. *J ECT* 2014; 30:91-93.

[28] For all my professional life I struggled with the labels, seeking ways to identify homogeneous populations. In later decades I studied concepts of melancholia and then catatonia, finding that these syndromes were identifiable, verifiable, and treatable, each with individual pathophysiologies.

[29] Such measurements were tedious. When I learned in 1959 about an electronic wave analyzer that was demonstrated by George Ulett, I obtained funding from NIMH and requested a model built by Ulett. The instrument was unstable and required as much detailed care as did hand measurements. In 1960, a digital computer analysis program for EEG was described. When I accepted a position in St Louis at the Missouri Institute of Psychiatry, I asked for funding for such a system. In 1963, an IBM 1710 system was leased and programs for period analysis and power spectrum analysis were developed. Quantitative digital EEG analysis was central to my continued interest in the effects of psychoactive drugs.

[30] Fink M, Kahn RL. Relation of EEG delta activity to behavioral response in electroshock: Quantitative serial studies. *Arch Neurol Psychiatry* 1957; 78:516-525.

[31] The experiments are extensively described in Fink M. *Convulsive Therapy: Theory and Practice*. NY: Raven Press, 1979.

[32] The mortality rate in modified ECT is less than the acknowledged rates for anesthesia for all other surgical procedures. Tørring N, Sanghania SN, Petrides G, Kellner CH, Østergaard SD. The mortality rate of electroconvulsive therapy:a systematic review and pooled analysis. *Acta psychiatr Scand* 2017; DOI: 10.1111/acps.12721

[33] Ulett GA, Johnson MW. Effect of atropine and scopolamine upon electroencephalographic changes induced by electroconvulsive therapy. *Electroencephalogr Clin Neurophysiol* 1957; 9:217-224. My interest in these studies introduced me to George Ulett who later enticed me to St Louis in 1962 to establish the Missouri Institute of Psychiatry.

[34] Denber HC. Electroencephalographic findings during chlorpromazine-diethazine treatment. *J Nerv Ment Dis* 1958; 126(4):392-8.

[35] Fink M. Effect of anticholinergic agent diethazine on EEG and behavior; significance for theory of convulsive therapy. *AMA Arch Neurol Psychiatry* 1958; 80(3): 380-7.

[36] Fink M. Cholinergic aspects of convulsive therapy. *J Nerv Ment Dis* 1966; 142:475-482.

[37] Korin H, Fink M, Kwalwasser S. Relation of changes in memory and learning to improvement in electroshock. Confin Neurol 1956;16:88-96.

[38] Kahn RL, Fink M, Weinstein EA. Relation of amobarbital test to clinical improvement in electroshock. *AMA Arch Neurol Psychiatry* 1956; 76(1): 23-9.

[39] Kahn RL, Fink M. Prognostic value of Rorschach criteria in clinical response to convulsive therapy. *J Neuropsychiatry* 1960; 1: 242-5.

[40] Kahn RL, Pollack M, Fink M. Social attitude (California F Scale) and convulsive therapy. J *Nerv Ment Dis* 1960; 130: 187-92.

[41] Ulett GA, Gleser GC, Caldwell BW, Smith K. The use of matched groups in the evaluation of convulsive and subconvulsive photoshock. *Bull Menninger Clin* 1954; 18:138-156;
Ulett GA, Smith K, Gleser GC. Evaluation of convulsive and subconvulsive shock therapies utilizing a control group. *Am J Psychiatry* 1956; 12:795-802.

[42] Crow TJ. The scientific status of electroconvulsive therapy. *Psychol Med* 1979; 9(3): 401-8.

[43] Palmer RL. *Electroconvulsive therapy: an appraisal*. NY: Oxford University Press, 1981.

[44] Lambourn J, Gill D. A controlled comparison of simulated and real ECT. In: Palmer RL (Ed): *Electroconvulsive therapy: an appraisal*, 1979; 17:193-201.

[45] Small, J. G., Small, I. F., Sharply, P., and Moore, D. F. A double-blind comparative evaluation of flurothyl and ECT. *Arch. Gen. Psychiatry*, 1968; 19:79-86.

[46] Kurland, A. A., Hanlon, T. E., Esquibel, A. J., et al. A comparative study of hexafluorodiethyl ether (Indoklon) and electroconvulsive therapy. *J. Nerv. Ment. Dis.* 1959; 129:95-98.

[47] Laurell, B. (Ed.): *Flurothyl convulsive therapy*. *Acta Psychiatr. Scand. [Suppl.]*, 213:1-79, 1970.

[48] Fink, M., Kahn, R. L., Karp, E., *et al*. Inhalant-induced convulsions: Significance for the theory of the convulsive therapy process. *Arch. Gen. Psychiatry* 1961; 4:259-266.

[49] Our conclusion that flurothyl seizures had no advantages of the electrical induction did not anticipate the hostility against electricity and ECT that marked the 1970s and 1980s, hostilities that would justify ambulatory clinic treatments with no connection to electricity.

[50] In the summer of 2014, a second year medical student, Kathryn Cooper from the University of Rochester, spent the summer on Long Island reviewing the flurothyl literature. Cooper K, Fink M. The chemical induction of seizures in psychiatric therapy: Were flurothyl (Indoklon) and pentylenetetrazol (Metrazol) abandoned prematurely? *J Clinical Psychopharmacology*. 2014; 34(5):602-7. Two other publications followed, a news article in the *Psychiatric Times* with Edward Shorter (Revive flurothyl inhalation treatment in psychiatry? *Psychiatric Times* March 19, 2014) and an invited essay on the role of the seizure and of electricity in induced seizure therapies. (Fink M. The seizure, not electricity, is essential in convulsive therapy: The flurothyl experience. *J ECT* 2014; 30:91-93).

[51] As I had no clinical base, I could not undertake the reassessment myself.

04: After Missouri Hiatus, Interest in Seizures Renewed 1966-

[1] Richard Abrams' psychiatric residency at New York Medical College in 1964 was interrupted by military service in the US Air Force 1965-67. He returned to complete his residency training 1967-69, was a NYMC Attending Psychiatrist 1969-1973, joined the faculty at Stony Brook 1973-1976 and then led the Chicago Medical School's Department of Psychiatry as vice-chairman from 1976 until his retirement in 1996.

[2] In retrospect, Abrams' conclusion of equivalent efficacy for the treatments with different electrode placements was a Type II statistical error, the dependence of a conclusion on inadequate sample size to determine small differences.

[3]Abrams R. Interview with Lothar Kalinowsky, M.D. *Convulsive Ther* 1988;4: 24-39;
Rzesnitzek L. 'A Berlin psychiatrist with an American passport': Lothar Kalinowsky, electroconvulsive therapy and international exchange in the mid-twentieth century. *History of Psychiatry* 2015; 26(4): 433-451.

[4] Blachly PH, Gowing D. Multiple monitored electroconvulsive therapy. *Comprehens Psychiatry* 1966; 7:100-109.

[5] NIMH grant 13358, a 4-year study titled "Quantitative EEG in Himan Psychopharmacology" beginning in 1971 at $60,000/year through the New York Medical College.
NIMH Grant 15561 titled "Theoretical, Clinical Studies of Convulsive Therapy" was a 3-year study at Gracie Square Hospital through the International Association for Psychiatric Research at $54,000/year.

[6] Abrams R, Fink M., Dornbush RL, Feldstein S, Volavka J. Unilateral and bilateral electroconvulsive therapy: Effects on depression, memory and the electroencephalogram. *Arch Gen Psychiatry* 1972; 27:88-91.

[7] For RUL treatments we identified the dominant side using the method of Lancaster that tested for eye, hand and foot dominance. The treatments were given using either the Medcraft B-24 or Reiter Mol-AC II alternating current devices. Lancaster NP, Steinert RR, Frost I. Unilateral electro-convulsive treatment. *J Ment Sci* 1958;104:221-227.

[8] Severity of depressive mood was rated by items on the 17-item Hamilton Rating Scale; memory effects were rated by three tasks – two auditory verbal and one visual non-verbal test; and EEG recordings were made before the first treatment and the day after the fourth treatment. To account for the multiple variables the data were evaluated using multiple stepwise regression analyses.

[9] Dornbush R, Abrams R, Fink M. Memory changes after unilateral and bilateral convulsive therapy. *Br J Psychiatry* 1971; 119:75-78.

[10] Abrams R, Volavka J, Roubicek J, Dornbush R, Fink M. . Lateralized EEG changes after unilateral and bilateral electroconvulsive therapy. *Dis Nerv Syst* 1970; 31 Suppl:28-33.

[11] Volavka J, Feldstein S, Abrams R, Dornbush R, Fink M. EEG and clinical change after bilateral and unilateral electroconvulsive therapy. *Electroenceph clin Neurophysiol* 1972; 32:631-639.

[12] Fink M, Kahn RL. Relation of EEG delta activity to behavioral response in electroshock: Quantitative serial studies. *Arch Neurol Psychiatry* 1957; 78:516-525.

[13] Abrams R, Volavka J, Fink M. EEG seizure patterns during multiple unilateral and bilateral ECT. *Comprehens Psychiatry* 1973; 14:25-25;
Volavka J, Feldstein S, Abrams R, Dornbush R, Fink M. EEG and clinical changes after unilateral and bilateral electroconvulsive therapy. *Electroenceph clin Neurophysiology* 1972; 32(6): 631-9.

[14] Abrams R, Fink M. Clinical experience with multiple electroconvulsive treatments. *Comprehens Psychiatry* 1972; 13:115-121.

[15] Later, when studying malignant catatonia, I successfully and rapidly treated febrile, physiologically compromised seriously ill patients with one or two seizures daily to ensure rapid resolution of the lethal condition.

[16] The lack of cases with poor outcomes among treated patients is a hurdle in identifying criteria for patient selection. The importance of failed cases in treatment assessments is thoroughly discussed by Richard Abrams in several editions of his textbook *Electroconvulsive Therapy* (New York: Oxford University Press)1988, 2002.

[17] Individual case reports are described in Fink M. *Electroshock: Restoring the Mind*. New York: Oxford University Press, 1999; and in the second edition titled *Electroconvulsive Therapy: A Guide for Professionals & Their Patients*, 2009.

[18] Moise F, Petrides G. Case study: electroconvulsive therapy in adolescents. *J Am Acad Child Adolesc Psychiatry* 1996; 35(3): 312-8

[19] Patient Claudia, page 89, Fink 1999.

[20] Thuppal M, Fink M. Electroconvulsive therapy and mental retardation. *J ECT* 1999; 15: 140-9.

[21] Patient Donald pg 91.

[22] Wachtel L, Dhossche D. Self-injury in autism as an alternate sign of catatonia: implications for electroconvulsive therapy. *Med Hypotheses* 2010; 75(1): 111-4.

[23] During the third trimester, when the fetus and placental fluids may press on the diaphragm and restrict breathing, mothers are placed in a lateral position. Antacids are administered pre-treatment to offset gastric reflux.

[24] Kiloh LG. Pseudo-dementia. *Acta Psychiatr Scand* 1961; 37:336-351.

[25] Bright-Long LE, Fink M. Reversible dementia and affective disorder. *Convulsive Ther* 1993; 9: 209-216.

[26] Fink M. Reversible and irreversible dementia. *Convulsive Ther* 1989; 5:123-125.

[27] Fink M. Delirious mania. *Bipolar Disorders* 1999; 1: 54-60.

[28] Malur C, Fink M, Francis A. Can delirium relieve psychosis? *Comprehens Psychiatry* 2000; 41: 450-453.

[29] Maltbie AA, Wingfield MS, Volow MR, Weiner RD, Sullivan JL, Cavenar JO. Electroconvulsive therapy in the presence of brain tumor. Case reports and an evaluation of risk. *J Nerv Ment Dis* 1980; 168(7):400-5.

[30]Greenberg LB, Mofson R, Fink M. Prospective electroconvulsive therapy in a delusional depressed patient with a frontal meningioma. A case report.*Br J Psychiatry*. 1988;153:105-7.

[31] Greenberg LB, Anand A, Roque CT, Grinberg Y. Electroconvulsive therapy and cerebral venous angioma. *Convulsive Ther*. 1986; 2(3):197-202.

[32] Petrides G, Fink M. Atrial fibrillation, anticoagulation, and electroconvulsive therapy. *Convulsive Ther*. 1996; 12: 91-98 .

[33] Bailine S, Petrides G, Doft M, Lui G. Indications for the use of propofol in electroconvulsive therapy. *J ECT* 2003; 19(3):129-32.

[34] Fink M, Johnson L. Monitoring the duration of ECT seizures: 'Cuff' and EEG methods compared *Arch Gen. Psychiat*. 1982; 39:1189-1191;
Greenberg LB. Detection of prolonged seizures during electroconvulsive therapy: A comparison of electroencephalogram and cuff monitoring. *Convulsive Ther*. 1985; 1(1):32-37.

[35] Calev A, Fink M, G. Petrides, A. Francis, L. Fochtmann, Caffeine pre-treatment enhances clinical efficacy and reduces cognitive effects of ECT. *Convulsive Ther* 1993; 9:95-100.

[36] Fink M. Electroshock revisited. *Amer Scientist* 2000; 88 (2): 162-167.

[37] American Psychiatric Association.. *Electroconvulsive Therapy*. Task Force Report 22. 200 pp. Washington D.C., 1978.

[38] Fink M. Is EST a useful therapy of schizophrenia? In J.P. Brady and H.K.H. Brodie (eds.): *Controversy in Psychiatry*. Philadelphia, W.B. Saunders Co., 1978; 183-193;
Fink M. EST and other somatic therapies of schizophrenia. In L. Bellak (ed.): *Disorders of the Schizophrenic Syndrome*. Basic Books, New York, 1979; 353-363.

[39] Fink M, Sackeim HA. Convulsive therapy for schizophrenia? *Schizophrenia Bull.* 1996; 221: 27-39.

[40] Fink M, Taylor MA, Shorter E, Vaidya NA. The failure of the schizophrenia concept and the argument for its replacement by hebephrenia: applying the medical model for disease recognition (with). *Acta Psychiatr Scand* 2010; 122: 173-183;
Shorter E, Fink M. . *Endocrine Psychiatry: Solving the Riddle of Melancholia* (with E.Shorter). Oxford University Press;
Fink M. Presidential Perspective: Defining clinical diagnoses by the medical model. In: Cottler L (Ed): *Mental Health in Public Health: The Next 100 Years*, NY: Oxford University Press, 2011: 278-281.

[41] Fink M. Clozapine andelectroconvulsive therapy. *Arch Gen Psychiatry* 1990; 47: 290-291.

[42] An explanation is seen in the seizure EEG pattern of clozapine. ECT augmented these changes. Fink M. Abnormal EEG effects of Clozapine." *J Neuropsych Clin Neuroscience* 1996; 8: 114-115.

[43] At the end of the NIMH study period, analyses failed to find significant benefits in the rating scales. Additional patients were tested. After much statistical manipulation of the data, a minimal benefit was described in reducing the PANSS positive symptoms. The data had been gone over repeatedly, on one occasion by my statistical colleague Peter Irwin, with a failure to find statistical significance for the data at that juncture. When a penultimate pre-publication draft was sent for my approval, now with multiple co-authors added, I was not impressed by the report and withdrew my name. While there is some added benefit to ECT addition it is modest, as it is with ECT

added to treatment with other neuroleptics. The belief of synergy for clozapine is undemonstrated since control trials with ECT alone were not done.

Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra NR, Kane JM, Sanghani S, Goldberg TE, John M, Mendelowitz A. Electroconvulsive therapy augmentation of clozapine-resistant schizophrenia: A prospective, randomized study. *Am J Psychiatry* 2015; 172(1): 52-8.

[44] Bolwig TG, Hertz MM, Paulson OB, Spotoft H, Rafaelson OJ. The permeability of the blood-brain barrier during electrically induced seizures in man. *Eur J Clin Invest* 1977; 7:87-93.

[45] Zervas IM, Greenberg LB, Suckow RF, Cooper T, Jandorf L, Fink M. Rat brain concentrations of fluphenazine during a course of electrconvulsive shock. *Convulsive Ther* 1990; 6(4): 273-278.

[46]Langer G, Neumark J, Koinig G, et al. Rapid psychotherapeutic effects of anesthesia with isoflurane (ES narcotherapy) in treatment-refractory depressed patients. *Neuropsychobiology* 1985; 14: 118–120.

[47] Greenberg L, Gage J, Vitkun S, Fink M. Isoflurane Anesthesia Therapy: A Replacement for **ECT** in Depressive Disorders? *Convulsive Ther* 1987;3(4):269-277.

[48]Weeks HR, Tadler SC, Smith KW, et al. Antidepressant and neurocognitive effects of isoflurane anesthesia versus electroconvulsive therapy in refractory depression. *PLoS One* 2013; 8:e 69809.

[49] Aronson TA, Shukla S, Hoff A. Continuation therapy after ECT for delusional depression: A naturalistic study of prophylactic treatments and relapse. *Convulsive Ther*. 1987; 3(4):251-259. 1987

[50] Fink M, Abrams R, Bailine S, Jaffe R. Ambulatory electroconvulsive therapy. Task force report of the association for convulsive therapy. *Convulsive Ther.* 1996; 12: 42-55.

[51] As a psychologist, he was not licensed to prescribe the medications or ECT treatment of patients, necessarily relying on hired qualified physicians.

[52] The Review committee headed by Jonathan O. Cole included Gary Figiel, Max Fink, Ranga R Krishnan, S. Craig Risch, and Charles Welch. The CORE study was funded by NIMH in 1997 in four facilities in a study program titled: "Continuation ECT vs Pharmacotherapy: Efficacy and Safety." The initial CORE collaborators were Max Fink (Stony Brook University, New York), Charles Kellner (Medical University, Charleston SC), Teri Rummans (Mayo Clinic, Rochester MN) and John Rush (University of Texas, Dallas TX).

In the 14 years of this endeavor, many personnel and site changes occurred. Max Fink was replaced by George Petrides, John Rush by Mustafa Husain, and Teri Rummans by Keith Rasmussen and then by Shirlene Sampson as Principal Investigators at their individual sites. The initial site at Stony Brook University was moved to the Long Island Jewish Hillside Hospital, and that at Medical University of South Carolina moved to the New Jersey School of Medicine in Newark NJ. Throughout the many years the overall direction of the study and the reports was supervised by Charles Kellner.

[53] CORE is the acronym for the Consortium for Research in ECT; we use CUC as the acronym for the Columbia University Consortium of various collaborating sites.

[54]Sackeim HA, Haskett RF, Mulsant BH *et al.* Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy. *JAMA* 2001; 285:1299–13

[55] Fink M. What was learned. Studies by the Consortium for Research in ECT. *Acta psychiatr Scand* 2014; 129: 417-426.

[56] The 6-month Continuation-ECT schedule was once weekly for four weeks, then biweekly for one month, and monthly thereafter. The NIMH review committee of our study thought that if we allowed clinicians the freedom to

use continuation treatments responsive to patient needs it would unduly advantage the ECT treatment group compared to the medication groups. But such argument was biased since the lithium-nortiptyline dosing schedules were monitored and modified according to serum blood levels and patient needs. This is one of many examples of the biases inserted in the design of NIMH supported studies by the members of review committees. Another adverse decision of the CORE application review committee was the rejection of our desire to measure the DST (dexamethasone suppression test) to identify the melancholic depressed in our samples.

[57] Fink M, Taylor MA. Electroconvulsive therapy: Evidence and challenges. *JAMA* 2007; 298: 330-332

[58]Bailine S, Fink M, Knapp R et al. Electroconvulsive therapy is equally effective in unipolar and bipolar depression. *Acta Psychiatr Scand* 2010; 121:431–436.

[59] The protocols for the treatment of bipolar depressed patients include trials of anticonvulsants, lithium, atypical neuroleptics, and complex combinations of these agents before considering ECT, commonly after five or more failed trials. Such guidelines have been proposed by the APA, various national and international psychopharmacologic societies. As a recent example see Goodwin GM, Haddad PM, Ferrier IN and 24 others. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association of Psychopharmacology. *J Psychopharmacol* 2016; 30(6):495-533.

[60]Kellner CH, Fink M, Knapp R *et al.* Relief of expressed suicidal intent by ECT: a Consortium for Research in ECT Study. *Am J Psychiatry* 2005; 162:977–982.

[61]Glassman AH, Kantor SJ, Shostak M. Depression, delusions, and drug response. *Am J Psychiatry* 1975; 132:716–719.

05 Electroshock in the Public Eye

[1] I had stimulated and financed Edward Shorter and David Healy to write a history of the shock therapies, introduced them to the world's leaders, and participated in many of the interviews. On publication we agreed that my co-authorship would identify the book as "promoting the shock therapies" and would disservice their work.

[2] Prolonged sleep therapy was introduced by Jakob Klaesi in 1922; insulin coma by Manfred Sakel in 1933; induced seizures by Ladislas Meduna in 1934, and leucotomy by Egas Moniz in 1936, each in Europe. So accepted was leucotomy that Moniz was awarded the Nobel Prize in Medicine in 1949.

[3] Shorter, Edward. *A History of Psychiatry*. New York: John Wiley & Sons, 1997.

[4] Gazdag G, Bitter I, Ungvari GS, Baran B, Fink M. László Meduna's pilot studies with camphor inductions of seizures: the first 11 patients.*J ECT.* 2009 Mar; 25(1):3-11.

[5] Yet, when I published my manual for patients, their families, and their physicians in 1999, I titled the book *Electroshock* to be recognized by a broader public. Similarly, when the historian Edward Shorter and the psychopharmacologist David Healy published their history of the treatment, they elected the title of *Shock Therapy:A History of Electroconvulsive Therapy in Mental Illness*. When Kitty Dukakis and Larry Tye published *SHOCK: The Healing Power of Electroconvulsive Therapy*, they also used the challenging name. Each of us hoped to weaken the hostility to the titles and believed that this term would be more widely recognized than any other title.

[6]Leon Eisenberg, an early pioneer in psychopharmacology at Harvard, once made the notable historical observation that "in the first half of the 20th century, American psychiatry was virtually 'brainless.' . . . In the second half of the 20th century, psychiatry became virtually 'mindless.' " The brainless period was a reference to psychiatry's early infatuation with psychoanalysis; the mindless period, to our current love affair with pills.

[7] Fink M. *Convulsive Therapy: Theory and Practice*. NY: Raven Press, 1979.

[8] Frankel FH. Electro-convulsive therapy in Massachusetts: A Task Force Report. *Mass Jrl Mental Health* 1973; 3(2): 3-29.

[9] Secretary (1957,1958), Chairman (1962). Sections organized sessions usually on single questions of interest. About 1964 the central Program Committee of the APA assumed responsibility for the whole program and the sections were disbanded.

[10] I invited colleagues to describe their experiences – how to optimize treatments (Richard Abrams), the effects of seizures on memory (Rhea Dornbush), electrophysiologic changes (Jan Volavka), flurothyl-induced seizures (Joyce and Iver Small of Indiana University), neurochemistry of seizures in animals (Walter Essman of Queens College), systemic medical issues associated with seizures (Ferris Pitts of Washington University), and my description of hypotheses of the mechanism of action. Earlier I had offered three different images of the mechanism by which induced seizures generated its benefits , but organizing this special number rekindled my interest in the issue. Fink M (Ed): *Convulsive Therapy. Seminars in Psychiatry*4:1. Grune & Stratton, Inc., New York, 70 pp.

[11] http://law.justia.com/cases/california/court-of-appeal/3d/57/662.html

[12] Restrictions on lobotomy had little effect on clinical care as the procedure had largely been supplanted by chlorpromazine and other neuroleptic drugs.

[13] Ottosson J-O, Fink M. *Ethics in Electroconvulsive Therapy*. NY: Brunner-Routledge, 2004.

[14] Clinician members were George Bidder and George Wayne of Los Angeles, Max Fink of Stony Brook, Michel Mandel of Massachusetts General Hospital, Iver Small of Indianapolis, and psychologist Larry R. Squire of the San Diego VA.

[15] American Psychiatric Association. *Electroconvulsive Therapy*. Task Force Report #14. Washington DC: APA, May 1978.

[16] The established diagnostic schema was the DSM-II published in 1965. Its inadequacies led the Association to undertake a new classification published in 1980 as the DSM-III.

[17] Abrams R, Fink M, Dornbush RL, Feldstein S, Volavka J, Roubicek J. Unilateral and bilateral ECT: effects on depression, memory and the electroencephalogram. *Arch. Gen. Psychiat.* 1972; 27: 88-94.

[18] This argument was experimentally confirmed in a comparison of two NIMH-supported parallel studies, one that used bilateral and one right unilateral electrode placement. The mean number of treatments was 7.0 for BT and 10.5 for unilateral. (Fink M, Taylor MA. Electroconvulsive therapy: Evidence and challenges. *JAMA* 2007; 298: 330-332)

[19] In the 1980s, when we became aware of the risks of the newer psychotropic drugs for persistent neurologic lesions, acute malignant catatonia syndromes, and systemic illnesses, I enquired whether prescribing physicians should offer patients a similar informed consent instrument for their voluntary signature. In repeated debates, psychiatric leaders refused to adopt such a practice. At the end, the Stony Brook Department Chairman Fritz Henn noted that despite the value of the argument, as department head he would not endorse such a procedure. (Max Fink Archives, Series 4- Professional Activities, Box 49, April 5, 1994.)

[20] My Task Force meeting files are at the Special Collections of the Stony Brook University Library. See Series 3, Boxes 62-64.

[21] Letters are in the Max Fink Archives, VI:Series 3, subseries 3, Box 62-64.

[22] Palmer RL. *Electroconvulsive Therapy: an appraisal*. New York: Oxford University Press, 1981.

[23] Fink M, Taylor MA. Electroconvulsive therapy: Evidence and challenges. *JAMA* 2007; 298: 330-332.

[24] Ottosson J-O, Fink M. *Ethics of Electroconvulsive Therapy*. New York: Brunner-Routledge, 2004.

[25] Abrams R. *Electroconvulsive Therapy*. New York: Oxford University Press, 1988, 2002.

[26] A decade later, when I was pre-occupied with editing the quarterly journal *Convulsive Therapy*, Richard Abrams assumed responsibility for its revisions and his text is now the established textbook.

[27] New York, Raven Press, 1979.

[28] In 2013, President Obama announced large-scale funding of a BRAIN Initiative, a collaboration of government, industry, and academia to study the functions of the human brain. The targets for research funding do not mention the effects of seizures. In a laudatory commentary Jeffrey Lieberman, President of the American Psychiatric Association, and a laboratory scientist, Cornelia Bargmann, suggest the aims for psychiatry: "*Can states of disturbed mental activity be stabilized with cognitive therapy, medications, or neuromodulatory or electroceutical interventions such as transcranial magnetic stimulation and deep brain stimulation?*" Their failure to consider induced seizures is consistent with the national disinterest in its mechanism. (Bargmann CI, Lieberman JA. What the BRAIN Initiative means for psychiatry. *Am J Psychiatry* 2014; 171:1038-1040)

[29] Meduna L. Autobiography. *Convulsive Ther.* 1985; 1:43-57; 121-35.

[30] In the journal. clinicians described their experiences with anesthetics and muscle relaxants, continuation out-patient treatments, augmenting seizures with caffeine and antipsychotics, the safe use of bite-blocs, treating patients with neurological and cardiovascular diseases, safety of treatments in pregnancy, changes in serum and CSF peptides, efficacy and safety of multiple monitored ECT (MMECT) and different electrode placements and their impact on memory tests, the use of EEG measures as evidence of an effective seizure and optimized treatment course, and the test of isoflurane anesthesia as a replacement for induced seizures.

[31] Charles Kellner, as editor, seeing the interest in brain stimulation and following the enthusiasm and financial investment of the members of the Association for Convulsive Therapy encouraged the change in the group's name to International Society for ECT and Neurostimulation (ISEN), and changed the journal title to *Journal of ECT and brain stimulation* (*J ECT*) with volume 14 in 1999.

[32] Tom Bolwig brought the early experience by Giovanni Aldini and Benjamin Franklin applying galvanic currents to the mentally ill. We published the story in Bolwig TG, Fink M: Electrotherapy of melancholia: The pioneering contributions of Benjamin Franklin and Giovanni Aldini. *J ECT* 2009; 25:15-18.

[33] Fink M. *Informed ECT for Patients and Families*. Videotape. Somatics, Inc. Lake Bluff IL, 1986;
Fink M. *Informed ECT for Health Professionals*. Videotape. Somatics, Inc. Lake Bluff IL, 1986

[34] Rick D'Alli went on to medical training graduating from the University of Arizona. He became an Associate Professor of Child Psychiatry and of Pediatrics at Duke University, and in 2016 he was at the University of Florida in Gainesville.

[35]Consensus Conference. Electroconvulsive therapy.*JAMA.* 1985 Oct 18;254(15):2103-8.

[36] Richard Weiner, Chairman; Max Fink, Donald Hammersley, Iver Small, and Louis Moench as members, with Harold Sackeim as consultant. American Psychiatric Association. *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging*. Washington DC: Americasn Psychiatric Association, 186 pp, 1990.

[37] The Association for Convulsive Therapy established a one-day teaching session on the day before the APA annual meetings. Certificates of attendance were presented and many institutions accepted such limited experience as sufficient for privileging physicians to administer ECT. On numerous occasions I argued that such an inadequate standard was a disservice to the institutions that needed guidance for privileging of professionals. The reversion to the early days of education by "see one, do one, teach one" was also an unprincipaled disservice to patients, and I protested such teaching. Fortunately ECT is a benign and uncomplicated procedure if done correctly, although bad outcomes are frequently recorded and have been the basis for malpractice complaints.

[38]Rouechè B. As empty as Eve. *The New Yorker,* September 9, 1974, pp. 84 –100.

[39]I was an expert witness for the defense in the malpractice suit she initiated; the Court sided with the physician after presentations of her many activities.

[40] Postgraduate teaching sessions in clinical psychiatry including ECT were organized by John Schwartz, a physician friend. He invited me to lecture on ECT in sessions organized in various cities over two decades. I also wrote a column on ECT for his monthly *Psychiatric Times* beginning in 1994 to the end of 2010.

[41] Linda Andre sued New York Hospital for malpractice for not warning her of the possible loss of memory when she was treated after a suicide attempt by drug overdose. I was a witness for the defense. The Court supported the use of ECT. We met often at public meetings and she delighted in attacking me at every meeting and in print. In 2009 she published her experiences in *Doctors of Deception: What They Don't Want You to Know about Shock Treatment* (New Brunswick, NJ: Rutgers University Press, 2009).

[42]<http://www.ectresources.org/ECTscience/Salters_2007_ECT_Malpractice_Case_Appeal_2007_Judges_Opinion_Supports_my_Testimony.pdf>
<http://ahrp.org/landmark-decision-jury-awards-635177-damages-for-memory-loss-from-electroshock/>

[43]Other complaints lodged in court cases about ECT included prolonged seizures in patients with pulmonary disease being treated with theophylline. The medication dosage should have been withheld or lowered before each treatment. Prolongation of the seizure requires intervention with a benzodiazepine and assurance of oxygenation by intubation. Failure to do so resulted in court challenges. Fink M, Sackeim HA. Theophylline and ECT. *JECT* 1998; 14:286-290.

[44] Houston Merritt, like many neurologists, abhorred the induction of seizures as a therapy. Neither teachers nor their students can overcome their primal anti-seizure attitudes. Merritt made his professional name by testing chemicals in the animal model of inducing seizures electrically, finding phenytoin raised seizure thresholds, and he encouraged its use as treatment for epilepsy.

[45] Quoted in Fink M. Bearing Witness: Personal and Poetic Descriptions of Seizure Therapy. *J ECT* 2016; 32(1):13-16.

[46] Bassett, K. *In Two Minds: A Biography of Jonathan Miller*. London: Oberon Books, 2012.

[47]Nasar S. *A beautiful mind*. New York: Simon & Shuster, 1998.

[48] Produced by Ron Howard with Russell Crowe playing John Nash, *A Beautiful Mind* portrayed the paranoia and obsessive repetitive behaviors of the illness and the seizures well. In retrospect, his illness would have had a better outcome had he been treated by ECT. Howard R, Hallowell T (producers). *A Beautiful Mind* [Film]. Universal Pictures/Dreamworks Pictures/Imagine Entertainment. 2001.

[49] Fink M. A *Beautiful Mind* and Insulin Coma; Social constraints on psychiatric diagnosis and treatment. *Harv Rev Psychiatry* 2003; 11:284-290.

[50] An obvious takeoff of the popular view in Europe and the United States that mentally ill were genetically inferior and best killed to improve the national gene pool. Sakel's insistence that seizures were not helpful was in response to the reports by Ladislas Meduna that chemically induced seizures were beneficial for schizophrenic patients, the same ones that Sakel targeted.

[51] Both Sakel's and Meduna's recommended treatments followed Wagner von Jauregg's therapeutic line of "one illness curing another" for which he was awarded the 1927 Nobel Prize for Medicine.

[52] This procedure effectively negates the clinical benefit of the first seizure since the dosing is inadequate, especially for unilateral electrode placements. The evidence is compelling that for RUL placements effective dosing requires a minimum of 6 to 8 times the ST. A more practical dosing schedule is based on patient age with verification by monitoring the EEG seizure duration and pattern. Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. *Convulsive Ther* 1996;12: 138-146. The best guide is an examination of the duration and pattern of the seizure. If the seizure EEG is less than 30 seconds and the pattern not clear for buildup, slow waves, slow waves and spikes, and a sharpend point, the stimulus can be immediately repeated under the same medications.

[53] McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects, *Arch Gen Psychiatry* 2000; 57(5): 438-44.

[54] Fink M, Taylor MA. Electroconvulsive therapy: Evidence and challenges. *JAMA* 2007; 298: 330-332.

[55] Fink M. What was learned: Studies by the Consortium for Research in ECT (CORE) 1997-2011. *Acta Psychiatrica Scand*. 129: 417-426.

[56] The first treatment in Sackeim's method identifies the seizure threshold. Assuming the adequacy of the multiplication factor for the energy, the succeeding treatments are thought to be "effective." But the choice of multiplier is a guess, the result only seen when the response of the patient is delayed or the treatment course is considered failed. The first seizure is necessarily ineffective, of no benefit to the patient. Such use is clearly unethical.

[57] When the British Royal College of Psychiatrists established an ECT certification system in 2003 known as ECTAS, it established RUL treatments, ST measurements, and two treatments weekly as the effective schedules. Early on, EEG monitoring of seizures was not considered necessary. A decade later the inefficacy of these recommendations was acknowledged with broader guidelines encouraged.

[58]*Convulsive Ther* 1989; 5(2): 207-304.

[59] Fink M. Transcranial magnetic stimulation is not a replacement for electroconvulsive therapy in depressive mood disorders. *JECT* 2011; 27:3-4.

[60] In another of the repeated meta-analyses of ECT and TMS the authors conclude: "ECT was the most efficacious treatment with the cumulative probabilities of being the most efficacious treatment being: ECT (65%), B[il]-rTMS (25%), R[UL]-rTMS (8%), and L[UL]-rTMS (2%)."
Chen JJ, Zhao LB, Liu YY, Fan SH, Xie P. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: A systematic review and multiple-treatments meta-analysis. *Behavior Brain Research* 2017; 320:30-36.

[61] Fink M. The seizure, not electricity, is essential in convulsive therapy: The flurothyl experience. *J ECT* 2014; 30:91-93.

06: The Enigma of How Seizures Alter Behavior

[1] Fink M. *Convulsive Therapy: Theory and Practice*. NY: Raven Press,1979.

[2] Fink M. A unified theory of the action of physiodynamic therapies. *J. Hillside Hosp.* 1957; 6: 197-206.

[3] Fink M. The mode of action of convulsive therapy: the neurophysiologic-adaptive view. *J. Neuropsychiat.* 1962;3: 231-233.

[4] Fink M. Cholinergic aspects of convulsive therapy. *J. Nerv. Ment. Dis.* 1962;142: 475-484.

[5] Davies B, Carroll BJ, Mowbray RM. *Depressive Illness. Some Research Studies.* Springfield IL: C.C Thomas, 1972.

[6] Papakostas Y, Fink M, Lee J, Irwin P, Johnson L. Neuroendocrine measures in psychiatric patients: Course and outcome with ECT. *Psychiatry Research* 1980;4: 55-64

[7] Fink M, Ottosson J-O. A theory of convulsive therapy in endogenous depression: Significance of hypothalamic functions. *Psychiatry Research* 1980; 2: 49-61.

[8] Fink M. *Convulsive Therapy: Theory and Practice*. NY: Raven Press, 1979.

[9] Fink M. Denial of blindness following cerebral angiography. *J. Hillside Hosp.,* 1956; 5: 238-245.

[10] Bender MB. *Patterns in Perception*. Springfield IL: C.C Thomas, 1952.

[11] Fink M, Kahn RL, Green MA. Experimental studies of the electroshock process. *Dis. Nerv. Syst.*, 1958; 19: 113-118.

[12] Weinstein E, Linn L, Kahn RL. Psychosis during electroshock therapy:Its relation to the theory of shock therapy. *Am J Psychiatry* 1952; 109:22-26.

[13] Amobarbital in 0.5 Gm in 10 ml distilled water injected at the rate of 1 ml/minute until nystagmus on lateral gaze, slurred speech, or errors in counting. Fink, 1979, pg 136.

[14] Fink M, Kahn RL, Weinstein EA. Relation of Amobarbital test to clinical improvement in electroshock. *Arch. Neurol. Psychiat. (Chic.)*, 1956; 76: 23-29.

[15] Fink M. A unified theory of the action of physiodynamic theories. *J Hillside Hosp* 1957; 6:197-206.

[16] Fink M. The mode of action of convulsive therapy: the neurophysiologic-adaptive view. *J Neuropsychiatry* 1962; 3:231-233.

[17] Fink M. Effect of anticholinergic agent, diethazine , on EEG and behavior: Significance for theory of convulsive therapy. *AMA Arch Neurol Psychiatry* 1958; 80:380-387.

[18] Ulett GA, Johnson MW. Effect of atropine and scopolamine upon electroenceph-alographic changes induced by electroconvulsive therapy. *Electroenceph clin Neurophysiol* 1957; 9:217-224.

[19] Fink M. Effect of anticholinergic compounds on post convulsive electroencephalogram and behavior of psychiatric patients. *Electroenceph clin Neurophysiol* 1960; 12:231-233.

[20] Cone W, Tower DB, McEachern D. Acetylcholine and neuronal activity in epilepsy. *JAMA* 1948; 73:59-63.

[21]Aird RB, Strait LA, Pace JW, Hrenoff MK, Bowditch SC. Neurophysiological effect of electrically induced convulsions. *Arch Neurol Psychiat* 1956; 75:371-378.

[22] Bornstein M. Presence and action of acetylcholine in experimental brain trauma. *J Neurophysiol* 1946;n 9:340-366.

[23] Fink M. The mode of action of convulsive therapy: the neurophysiologic-adaptive view. *J. Neuropsychiat.*, 1962; 3: 231-233.

[24] Fink M. Cholinergic aspects of convulsive therapy. *Jrnl Nerv Mental Dis* 1966; 145(5): 475-484.

[25]The Karolinska Institute awarded the Nobel Prize in Physiology or Medicine for 1977 jointly to Roger Guillemin and Andrew Schally for their discoveries concerning "the peptide hormone production of the brain" and to Rosalyn Yalow for "the development of radioimmunoassays of peptide hormones."

[26] Loosen PT. The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. *Psychoneuroendocrinology* 1985;10(3):237-60.

[27] Papakostas Y, Fink M, Lee J, Irwin P, Johnson L. Neuroendocrine measures in psychiatric patients: course and outcome with ECT. *Psychiatry Res* 1981; 4(1): 55-64.

[28] Davies B, Carroll BJ, Mowbray RM. *Depressive Illness. Some Research Studies.* Springfield IL: C.C Thomas, 1972.

[29]*Idem*. Pp 128-137.

[30] Yiannis Papakostas was the first of three fellows that joined my studies from Athens. He returned to Athens when asked by the chairman Costas Stefanis. He was followed by Ioannis Zervas and Georgios Petrides. Each developed dedicated research studies and maintained academic careers.

[31] Papakostas Y, Fink M, Lee J, Irwin P, Johnson L. Neuroendocrine measures in psychiatric patients: course and outcome with ECT. *Psychiatry Res* 1981; 4(1): 55-64.

[32] Fink M. *Convulsive Therapy: Theory and Practice*. NY: Raven Press, 1979.

[33] Fink M, Sackeim HA. Convulsive therapy for schizophrenia? *Schizophrenia Bull.* 1996; 221: 27-39.

[34] Nemeroff CB, Bissette G, Akil H, Fink M. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry* 1991; 158: 59-63.

[35] Fink M, Kety S, McGaugh J. *Psychobiology of Convulsive Therapy*. Washington DC: V.H. Winston & Sons, 1974.

[36]*Ibid.*, Kety S. Chap 22, pg 285.

[37] For example, the fall in serum Ca^{++} levels with seizures supports the neuroendocrine mechanism. Flach F. Calcium metabolism in states of depression. *Br J Psychiatry* 1964; 110:588-593.

[38] In 2014 the *Journal of ECT* published numerous invited essays to explain the mode of action of induced seizures. None were well founded. It is remarkable that not one of the extensively funded neuroscience centers nor governmental agencies has taken on the question of the brain function mechanisms of this remarkable treatment.

[39] The Conference proceedings were not published. A copy of the official transcript is available in the Max Fink Archives, Stony Brook University Special Collections.

[40] Fink M, Ottosson J-O. A theory of convulsive therapy in endogenous depression: Significance of hypothalamic dysfunction. *Psychiatry Research* 1980; 2:49-61.

[41] I adopted this hypothesis as the most salient in presentations in 1984 at a plenary lecture on the mechanism of convulsive therapy at the CINP meeting in Florence, Italy. It was at that meeting that Alan Edelson of Raven Press invited me to establish a journal, and in 1985 the inaugural issue of the quarterly journal *Convulsive Therapy* appeared.

[42]Electroconvulsive Therapy. *NIH Consensus Statement* 1985 Jun 10-12; 5(11):1-23; also *JAMA* 1985; 254(15): 2103-8.

[43] In the CORE studies we carefully measured the seizure thresholds and could not confirm the rise. (Fink M, Petrides G, Kellner CH, *et al*. Change in seizure threshold during ECT: A CORE study. *J ECT* 2008; 24:114-116.) Nor can I envision how such a physiologic change (should it occur) would be an explanation for the therapeutic benefits.

[44]*Convulsive Ther* 1989; 5: 207-304.

[45] Sackeim HA. The unique contributions of ECT to understanding the pathophysiology and treatment of affective disorders. *Convulsive Ther* 1989; 5: 207-215.

[46] Lichtenberg P, Lerer B. Implications of clinical spectrum for mechanism of action: ECT and antidepressants reconsidered. *Convulsive Ther* 1989; 5: 216-226.

[47] Mukherjee S. Mechanisms of the antimanic effect of electroconvulsive therapy. *Convulsive Ther* 1989; 5: 227-243.

[48] Abrams R. Lateralized hemispheric mechanisms and the antidepressant effects of right and left unilateral ECT. *Convulsive Ther* 1989; 5: 244-249.

[49] Fink M, Nemeroff CB. A neuroendocrine view of ECT. *Convulsive Ther* 1989; 5: 296-304.

[50] "The broadly drawn hypotheses that ECT exerts its beneficial effects in depression through hypothalamic mechanisms . . . or by transmitter release, otherwise unspecified . . . are not specific enough to be heuristic -- or in the latter case –even untestable; and the more specific hypotheses . . . are either too narrow, premature or just plain wrong. Modern ECT researchers, regardless of their species of predilection, do not have any more of a clue to the relationship between brain biological events and treatment response in ECT than they did at the time of the first edition of this book – which is to say none at all. Moreover, modern theories of the action of ECT – even as formulated by sophisticated investigators with impeccable credentials –have not surpassed in conceptual elegance the 18th century claim that things burned because they contained phlogiston: ECT awaits its Lavoisier." Abrams R. *Electroconvulsive Therapy*. 2nd Edition. NY: Oxford University Press, 1992.

[51] Lerer B. The neurobiology of ECT: The road taken. *J ECT* 1998; 14(3): 149-152.

[52] Mann JJ. Neurobiological correlates of the antidepressant action of electroconvulsive therapy. *J ECT* 1998; 14(3): 172-180.

[53] Duman RS, Vaidya VA. Molecular and cellular actions of chronic electroconvulsive seizures. *J ECT* 1998; 14(3): 181-193.

[54] Sackeim HA . The anticonvulsant hypothesis of the mechanism of action of ECT: Current status. *J ECT* 1999; 15(1): 5-26.

[55] Sienaert P. Mechanisms of ECT. Reviewing the science and dismissing the myths.
J ECT 2014; 30: 85-86.

[56] *JECT* 2014; 30:85-175.

[57] Fink M. The seizure, not electricity, is essential in convulsive therapy. *J ECT* 2014; 30: 91-93.

[58] Haskett RF. Electroconvulsive therapy's mechanism of action: Neuroendocrine hypothesis. *J ECT* 2014; 30(2): 107-110.

07 Introducetion to Clinical Psychopharmacology

[1] Fink M, Shaw R, Gross G, Coleman FS. Comparative study of chlorpromazine and insulin coma in the therapy of psychosis. *JAMA* 1958; 166:1846-1850.

[2] Herman Denber at Manhattan State Hospital, Sidney Merlis at Central Islip Psychiatric Center, and Sidney Malitz at the NY State Psychiatric Institute in NY; Enoch Callaway in San Francisco, Charles Shagass in Philadelphia, Arthur Sugerman in New Jersey; Dieter Bente and Turan Itil in Erlangen, Germany; Pierre Etevenon in Paris, France--each managed an EEG Laboratory to study the drug effects of psychotropic drugs in the psychiatric ill.

[3] The search for effects in animals is exemplified by the apocryphal story of an observer, seeing a drunk man stumbling and searching the ground, asking "What are you looking for?"
"My keys."
"Where did you lose them?"
"Over there," pointing to the dark field.
"Why are you looking here?"
"Because the light is here."

[4] Weinstein EA, Kahn RL. *Denial of Illness*. Springfield IL: Charles C Thomas, 1955.

[5] Weinstein EA, Linn L, Kahn RL. Psychosis during electroshock therapy: Its relation to the theory of shock therapy. *Am J Psychiatry* 1952; 109: 22-26.

[6] Fink M, Kahn RL, Weinstein EA. The "Amytal test" in patients with mental illness. *J. Hillside Hosp.* 1955; 4*:* 3-13.

[7] Charles Shagass received his BS in psychology and MD at McGill University in 1952. For the next six years he organized an electrophysiology laboratory at the Allan Memorial Institute, moving to Temple University 1966 after stops in Iowa. He was a proponent of the medical model in psychiatry and the merits of quantitative EEG. He died in 1993.

[8] Shagass C. The sedation threshold; a method for estimating tension in psychiatric patients. *Electroencephalogr Clin Neurophysiol.* 1954; 6(2):221-33.

[9] Fink M. Lateral gaze nystagmus as an index of the sedation threshold. *Electroenceph. Clin. Neurophysiol.*, 1958; 10: 162-163.

[10] Fink M, Taylor MA. *Catatonia: A Clinician's Guide to Diagnosis and Treatment*. NY: Cambridge University Press, 2003.

[11] Wachspress M, Blumberg A, Fink M, Miller JSA. Evaluation of high dose reserpine. *J Hillside Hosp* 1956; 5(2): 67-88.

[12] The effects on liver functions were ascribed to contaminants in the initial batch of chemicals. The effects were measurable but not considered dangerous. In about a year, the liver dysfunction signs were no longer seen.

[13] Swartz MS, Stroup TS, McEvoy JP, Davis SM, Rosenheck RA, Keefe RS, Hsiao JK, Lieberman JA. What CATIE found: results from the schizophrenia trial. *Psychiatr Serv*. 2008: 59(5):500-6.
Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? *Br J Psychiatry*. 2008 Mar;192(3):161-3.)

[14] Fink M, Shaw R, Gross G, Coleman FS. Comparative study of chlorpromazine and insulin coma in the therapy of psychosis. *JAMA* 1958; 166:1846-1850.

[15] Nasar S. *A Beautiful Mind*. New York: Simon and Schuster, 1998.

[16] Doroshow DB. Performing a cure for schizophrenia: insulin coma therapy on the wards. *J Hist Med Allied Sci* 2007; 62(2): 213-43.

[17] Fink M. *A Beautiful Mind* and insulin coma: Social constraints on psychiatric diagnosis and treatment. *Harvard Review of Psychiatry* 2003; 11:284-290.

[18] The insulin coma unit had been an air-conditioned large suite on the second floor of the Lowenstein pavilion. The space was assigned to the staff members of the growing Department of Experimental Psychiatry and was used until a new building supported by a grant of the Ford Foundation was built about 1963.

[19] Fink M. Quantitative electroencephalography in human psychopharmacology II: drug patterns. In G. Glaser (ed.), *EEG and Behavior*. Basic Books, Inc., New York, 177-197, 1963.

[20] Fink M. Effect of anticholinergic agent, Diethazine, on EEG and behavior: significance for theory of convulsive therapy. *Arch. Neurol. Psychiat. (Chic.)*, 1958; 80: 380-387.

[21]Fink M. Effect of anticholinergic compounds on post-convulsive electroencephalogram and behavior of psychiatric patients. *Electroenceph. Clin. Neurophysiol.*, 1960, 12: 359-369.

[22] Fink M. Cholinergic aspects of convulsive therapy. *Jrnl Nerv Mental Dis* 1966; 145(5): 475-484.

[23] Fink M. Electroencephalographic and behavioral effects of Tofranil. McGill University Conference on Depression and Allied States. *Can Psych Assoc J*. 1959; 4:S166-S171.

[24] Fink M. Cholinergic aspects of convulsive therapy. *Jrnl Nerv Mental Dis* 1966; 145(5): 475-484.

[25]Dosages were 75-150-225-300 mg for imipramine; 300-600-900-1200 mg for chlorpromazine with 3.75-7.5-11.25-15 mg procyclidine added. Equal amounts of vehicle were used for placebo-treated patients.

[26] Fink M, Kahn RL. Behavioral patterns in convulsive therapy. *Arch. Gen. Psychiat.*, 5*:* 30-36;
Klein DF, Fink M. Psychiatric reaction patterns to Imipramine (Tofranil). *Amer. J. Psychiat.*, 1962:119: 432-438;
Klein DF, Fink M. Behavioral reaction patterns with Phenothiazines. *Arch. Gen. Psychiat.*, 1962; 7: 449-459*;*
Fink M, Klein DF, Kramer JC. Imipramine as an adjunct to Phenothiazine therapy. *Comprehens. Psychiat.*, 1962; 3: 377-380;
Fink M, Klein DF, Kramer J. Clinical efficacy of Chlorpromazine-Procyclidine combination, Imipramine and placebo in depressive disorders. *Psychopharmacolgia (Berl.)*, 1965; 7: 27-36;
Pollack M, Klein DF, Willner A, Blumberg AG. Imipramine-induced behavioral disorganization in schizophrenic patients: physiological and psychological correlates. In J. Wortis (ed.), *Biological Psychiatry*. Plenum Press, Inc., New York, 1965; 7: 53-6l;
Fink M. QuantitativeEEG and human psychopharmacology, III: changes on acute and chronic administration of Chlorpromazine, Imipramine and placebo saline. In W. P. Wilson: *Applications of Electroencephalography in Psychiatry*. Duke University Press, Durham, North Carolina, 226-240.

[27] Kahn RL, Fink M. Perception of embedded figures after induced altered brain function. *American Psychologist*, 1957; 12*:* 361;

Kahn RL, Pollack M, Fink M. Social factors in selection of therapy in a voluntary mental hospital. *J. Hillside Hosp.*, 1957; 6: 216-228;

Pollack M, Kahn RL, Fink M. Psychological factors affecting individual differences in behavioral response to convulsive therapy. *J. Nerv. Ment. Dis.*, 1959; 128: 243-248;

Jaffe J, Kahn RL, Fink M. Changes in verbal transactions with induced altered brain function. *J. Nerv. Ment. Dis.*, 1960; 130: 235-239;

Pollack M, Kahn RL, Fink M. Social attitude California F Scale and convulsive therapy. *J. Nerv. Ment. Dis.*, 1960; 130: 187-192;

Kahn RL, Pollack M, Fink M. Figure-ground discrimination after induced altered brain function. *Arch. Neurol. (Chic.)*, 1960; 2: 547-551;

Kahn RL, Fink M. Prognostic value of Rorschach criteria in clinical response to convulsive therapy. *J. Neuropsychiat.*, 1960; 1: 242-245.

[28] Fink M. Quantitative electroencephalography and human psychopharmacology: I. Frequency spectra and drug action. *Med. Exp. (Basel)*, 1961; 5: 364-369.

[29] Lorr M, O'Connor JP, Stafford JW. The psychotic reaction profile. *J Clin Psychol* 1960; 16:241-245.

Lorr M, Jenkins RL, Holsopple JQ. Multidimensional scale for rating psychiatric patients. *Veterans Adm Tech Bull 10,507*. VA, Washington DC, 1953.

[30] Fink M, D.F. Klein, Kramer J. Clinical efficacy of Chlorpromazine-Procyclidine combination, Imipramine and placebo in depressive disorders. *Psychopharmacolgia (Berl.)*, 1965; 7: 27-36.

[31] Klein DF, Fink M. Psychiatric reaction patterns to Imipramine (Tofranil). *Am. J. Psychiatry* 1962; 119: 432-438.

[32] Fink M, Kahn RL. Behavioral patterns in convulsive therapy. *Arch. Gen. Psychiat.*, 1962; 5: 30-36.

[33] Klein DF, Fink M. Behavioral reaction patterns with Phenothiazines. *Arch. Gen. Psychiat.*, 1962; 7: 449-459.

[34] Klein DF, Fink M. Psychiatric reaction patterns to Imipramine (Tofranil). *Amer. J. Psychiat.*,1962; 119: 432-438.

[35] Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961; 118:549-550.

[36] Hoffer A, Osmond H. *The Hallucinogens*. New York: Academic Press, 1967.

[37] Fink M, Itil T. Neurophysiology of the Phantastica: EEG and Behavioral Relations in Man. In: D. Efron, J. Cole, J. Levine and J.B. Wittenborn (eds.): *Psychopharmacology: A Review of Progress*, 1957-1967: U.S. Govt. Printing Office, Washington, DC, pp. 1231-1239.

[38]*New York Tim*es, Letters, Nov 15, 1957, page 26.

[39]*New York Times*, John W. Finney, Jan 15, 1958, pg 15.

[40] Nathan Kline was an early exuberant and enthusiastic researcher in psychopharmacology. In 1952 he organized the research services at Rockland Psychiatric Center in Orangeburg, NY and was among the first to describe the activities of chlorpromazine. He was a leader in the ECDEU program. He received prestigious Lasker awards for his studies of reserpine and another for iproniazid, an example of a new class of monoamine oxidase inhibitors, reporting both as antidepressants. He was a President of the American College of Neuropsychopharmacology and a leader in encouraging drug research in third-world countries. He was a good friend, encouraging me as a younger investigator.

In later years I was sent to Rockland as a member of a large NIMH grant review. Reviewing his charts we found that he examined multiple new substances simultaneously. In later years he promoted the study of clozapine despite the reports of its toxicity of white blood cells. After he died in 1983 his Rockland Psychiatric Center laboratories were renamed the Nathan S. Kline Institute.

[41] Years later, both Alfred Freedman and Stanley Yolles, Psychiatry Department chairmen with whom I worked, visited the Russian institutes and reported that the diagnosis was indeed used to incarcerate Russian dissidents.

[42] Soviet contributions to clinical psychopharmacology, EEG, and electroshock have been very limited. The Russian scholar Alexander Nelson authored a textbook, *Electroconvulsive Therapy in Psychiatry, Neurology and Addictive Medicine*, Moscow: BINOM Laboratory of Knowledge, 2005. It is based on Richard Abrams's *Electroconvulsive Therapy* (NY: Oxford University Press, 2nd Edition 2002).

08 Psychopharmacology: The St. Louis Interlude

[1] The St Louis State Hospital Medical Director, Louis Kohler installed himself and his administrative staff on the Institute Building. His unhappiness that his prized new building was taken away for research studies caused me and the Institute personnel much discomfort and conflict. I soon experienced the complex maneuverings necessary to manage state government funds, the rigidities of the personnel of the agencies, and Kohler's Mussolini-like attitudes. He very much resented our residence in the Institute building on the grounds of his hospital, insisting that his office be on the first floor of the new building. I was authorized to use a state car and he repeatedly criticized my parking. On an occasion when my wife drove the car to the Institute, he reported me to the authorities as abusing the State privilege.

[2] Nina Matheson established the MIP Medical Library. After 7 years at the MIP, Nina went on to be the Director of the Himmelfarb Health Sciences Library at George Washington University, then the National Library of Medicine Extramural Program, the Welch Medical Library at Johns Hopkins Medical School. She is author of the Matheson Report of the Association of Medical Colleges that set guidelines for the broadening of librarians beyond cataloguers to facilitators of research designs and studies.

[3]*Electroenceph Clin Neurophysiol* 1964; 16: Suppl 23, 68 pp.

[4] Lincoln TX-O, 65,000 words of memory and 6 micro-second per memory cycle. Using recorded EEG played through an Analog-to-Digital converter with the words stored in the memory for statistical processing. Farley BG. Recognition of patterns in the EEG. In: MA Brazier (Ed.): *Computer Techniques in EEG Analysis. EEG Clin Neurophysiol* Suppl 20; 49-55, 1961.

[5] In 1962 I approached the head of the Washington University Computer Center with my desire to develop a digital computer center and programming for EEG analysis. Donald Shapiro, a graduate student, accepted the challenge. His thesis was on the traveling salesman problem. He developed the IBM 1710 program in St. Louis. When I moved to New York, he followed me and set up IBM 1800 Center at 5 East 102 Street with his family in Great Neck. When I left the College he moved to the NYMC Westchester facility as Director of the Computer Center. Calm and steady, not perturbed by crises, his statistical skills developed the necessary filter, recording, and analysis programs for our pharmaco-EEG program. Don and his wife June supported the research by membership on the Board of the International Association for Psychiatric Research.

[6] The programs and their logic were published in "Quantitative Analysis of the Electroencephalogram by Digital Computer Methods" by Donald Shapiro and Max Fink in collaboration with Connie Hickman BSEE and Turan Itil, M.D. Copies are in the Max Fink Archives at Stony Brook University.

[7] Irwin, P. and Fink M. An empirical comparison of three EEG digital conversion techniques: baseline cross analysis, power spectral density analysis and Hjorth analysis. In: *Quantitative Analysis of the EEG*, M. Matejcek and G. K. Schenk (Eds.), AEG Telefunken, Konstanz, West Germany, pp. 379-393, 1976.

[8] We sought to establish a single overall measure of change in the EEG of drug effects without inflating statistical probability by testing the multiple interdependent variables that these quantification algorithms generated. Irwin, P. Spectral difference index: a single EEG measure of drug effect. *Electroenceph. clin. Neurophysiol*. 54:342-346, 1982.

[9] Turan M. Itil, founder of the science of pharmaco-EEG, developed the methodology to measure and classify psychoactive drugs by their impact on EEG frequencies and patterns. Educated in Turkey, neurology training under Prof F Flügel in Erlangen, Germany, he joined me in 1963 to establish the EEG laboratories of the MIP. When he joined MIP, he had published 44 reports. He married Ellen in Germany and they had two children, Kurt and Yasmin. When I left for New York he remained in St Louis moving to New York to replace me in the New York Medical College with Alfred Freedman. He died in 2014. Fink M. In Memoriam: Turan M. Itil. *Neuropsychopharmacology* 2014; **39,** 3133–3134.

[10] Fink M. *Pharmaco-electroencephalography: A debate in psychopharmacology*. In T. Ban, D. Healy, E. Shorter (eds.): *The Rise of Psychopharmacology and the Story of the CINP*, 1998; 151-6. Animula Publishing House, Budapest.

Fink M. A clinician-researcher and ECDEU: 1959-1980. In T. Ban, D. Healy, E. Shorter (eds.): *The Triumph of Psychopharmacology and the Story of the CINP*. Budapest, Animula, 2000, 82-96, 2000.

[11] Samuel Gershon graduated from the University of Sydney in 1950, received his DPM from the University of Melbourne in 1956, becoming Associate Professor in Pharmacology and Chairman in 1962. His early studies were of the pharmacology of lithium following the finding of clinical benefit for control of mania by John Cade. Desirous of coming to the US, he was recommended to the MIP by Jonathan O. Cole at NIMH. He developed pharmacology laboratories studying the anticholinergic Ditran and the cholinesterase inhibitor tetrahydroaminacridine (THA, Tacrine). He left MIP in 1966 for New York University and then appointments at University of Pittsburgh and University of Florida in Miami. He launched the journal *Bipolar Disorders* in 1999. He and his wife Lisl remained good friends.

[12]In addition to Turan Itil the clinicans included Sol Garfield Ph.D., Andy Don, Ivan Sletten, M.D., Ali Keskiner, M.D., Joseph Holden MBBS, , Harry Neurbauer, MBBS, Jovan Simeon, MD , Waheedul Haque MD, and Nafi KiremitciMD, clinicians recently emigrated to the US from Turkey, Greece and South Africa. Jovan joined me in New York.

[13] Keskiner A, Simeon J, Fink M, Itil TM. Long acting phenothiazine (fluphenazine Decanoate) in the treatment of psychosis. *Arch gen Psychiatry* 1968; 18:477-481.

[14]A systematic random controlled trial of thioridazine with or without chlordiazepoxide in our in-patients failed to find an additional benefit for the combination. Holden J, Itil T, Keskiner A, Fink M. Thioridazine and chlordiazepoxide, alone or combined, in the treatment of chronic schizophrenia. *Comprehens Psychiatry* 1968; 9:633-643.

[15] Butaperazine was marketed as Repoise by A. H. Robins who made large supplies freely available for these trials.

[16] Keskiner A, Itil TM, Todt N. A comparative study of butaperazine , chlorpromazine, and placebo in chronic schizophrenics. *Psychosomatics* 1970; 11(2): 120-6.

[17] Holden JM, Itil TM, Keskiner A. The treatment of lobotomized schizophrenic patients with butaperazine. *Curr Therap Res Clin Exp* 1969; 11(7):418-28.

[18] Edwin Gildea was appointed Chairman of Psychiatry and Neurology at Washington University in 1942. At George Ulett's request he agreed to affiliate the professional; appointees to the MIP to his Department, and appointed me as Research Professor. On his retirement in 1963, Eli Robins became the Chairman. Gildea was broadly trained and associated the Department with various hospitals in St. Louis.

[19] Eli Robins, a MD graduate of Harvard in 1943, joined the Department in 1949 dedicating his interest in the laboratory sciences. He became chairman in 1963. He consolidated the Department by cutting connections with the City, State and private hospitals in St. Louis. He went on to support the medical model of diagnosis in psychiatry, writing classic studies with Sam Guze, George Winokur and other leaders at the time. He was central to the development of DSM-III. His failure to support the staff of the MIP resulted in the Institute's demise.

[20] The Psychiatric Research Foundation of Missouri was a non-profit association of community supporters who funded Institute projects and supported its research by managing the Institute's funds and its Institutional Review Board. When I moved to New York I established a similar non-profit foundation, the International Association for Psychiatric Research, organized by Arnold and Phyllis Canter, Joshua Vogel, Laura and Ted Israel, Alice and Martin Green, Blanche and Melvin Muroff, Donald Shapiro, and Martha Fink. The Association supported my research until the mid-1980s when its funds were reincorporated in the Scion Natural Science Association as a non-profit family foundation.

[21] The initial budget for the MIP was $318,000 for the 1966-1968 biennium with assurance that the funding would increase to $1,000,000 for the next biennium. By the fall of 1964, we had received Federal and private funding to more than $800,000 annually. These funds were processed by the State and the legislative leaders then argued that our overall budget met the Governor's promises, did they not?

[22] The MIP has been converted to a teaching division of the University of Missouri for the training of psychiatric residents. The MIP building and the original state hospital buildings have been torn down and replaced by cottages for 200 clients and renamed the St Louis Psychiatric Rehabilitation Center.

09 Opioid and Cannabis Studies

[1] Soon after Alfred Freedman assumed responsibility for the Department, the building assigned to his use showed wall and basement fractures that led to its condemnation and closing. Offices were leased at 5 East 102 Street, a garage and office building in which I established my digital computer EEG laboratory and teaching offices.

[2] Decades earlier Manfred Sakel in Berlin sought to relieve the nausea, vomiting and weight loss in heroin detoxification by administering insulin. His patients became calmer and the withdrawal was less painful and uncomfortable. When he moved to Vienna in 1933, his experience encouraged him to use insulin to sedate psychotic and aggressive schizophrenic patients, and in the process he developed Insulin Coma Therapy.

Sakel M. *Neue Behandlungmethode der Schizophrenie*. Vienna: Moritz Perles Verlag, 1935.

Sakel M. *The Pharmacological Shock Treatment of Schizophrenia*. New York: Nervous and Mental Disease Publishing Co., 1938; translated by J. Wortis.

[3] Richard Resnick graduated New York Medical College and took his residency training at Hillside in 1950s. He was an active participant in the Hillside medication research programs, and volunteered for the LSD experiments. He joined me at NYMC when I returned in 1966. He actively studied heroin, methadone, naloxone and cyclazocine, and enjoyed the challenges of dealing with opiate dependent subjects. In the 1970s, he opened an office in Manhattan and for many decades maintained a private practice that treated opiate addiction with buprenorphine. He became an active member of the ACNP.

[4] Arthur Zaks obtained his MD at New York University in 1964 and his residency at New York Medical College. He collaborated in the heroin, naloxone, methadone studies and opened clinics for treatment of addiction in Brooklyn and maintained an active program until his death in 2014.

[5] Zaks A, Bruner A, Fink M, Freedman A. Intravenous diacetylmorphine (Heroin) in studies of opiate dependence. *Dis Nerv Syst Suppl* 1969; 30:89-92;

Volavka J, Zaks A, Roubicek J, Fink M. Electrographic effects of diacetylmorphine (Heroin) and naloxone in man. *Neuropharm* 1970; 9: 587-593.

[6] I received governmental permits to manufacture, prescribe, study, import and export opioids, opioid antagonists, cannabis, and cannabis products, hallucinogens and other restricted substances from the Federal Government Bureau of Narcotics and Dangerous Drugs, New York State Narcotic Addiction Control Commission, the International Drug Control Program of the World Health Organization, and the Greek government Import and Export commission.

[7] Freedman AM, Fink M, Sharoff R, Zaks A. Cyclazocine and methadone in narcotic addiction. *JAMA* 1967; 202:191-194.

[8] Zaks A, Fink M, Freedman AM. Duration of methadone induced cross-tolerance to heroin. *Br J Addiction* 1971;66:205-8

[9] Zaks A, Fink M, Freedman AM. Levomethadyl in maintenance treatment of opiate dependence. *JAMA* 1972; 220: 811-813.

[10] Dole VP. Comments on "heroin maintenance." *JAMA* 1972; 220(11): 1493.

[11] Fink M. Heroin maintenance. *JAMA* 1972; 221:602; *ibid. Contemp Drug Probl* 1972; 1: 875-877.

[12] http://www.slate.com/articles/news_and_politics/dispatches/features/2010/the_vancouver_experiment/does_it_work.html

[13] Freedman AM, Fink M, Sharoff R, Zaks A. Cyclazocine and methadone in narcotic addiction. *JAMA* 1967; 202:191-194;
Freedman AM, Fink M, Sharoff R, Zaks A. Clinical studies of cyclazocine in narcotic addiction. *Am J Psychiatry* 1968; 124:1499-1504.

[14] Resnick R, Fink M, Freedman AM. Cyclazocine typology in opiate dependence. *Am J Psychiatry* 1970; 126(9): 1256-60;
Resnick R, Fink M, Freedman AM. Cyclazocine therapy of opiate dependence. *Comprehens Psychiatry* 1971; 12:491-502.;
Resnick R, Fink M, Freedman AM. High dose cyclazocine therapy of opiate dependence. *Am J Psychiatry* 1974; 131:595-7.

[15] Fink M, Simeon J, Itil T, Freedman AM. Clinical antidepressant activity of cyclazocine – a narcotic antagonist. *Clin Pharmacol Ther* 1970; 11(1): 41-8.

[16] Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961; 118:549-550.

[17] Martin WR. Naloxone. *Ann Intern Med* 1976; 85(6):765-8.

[18] Zaks A, Jones T, Freedman AM, Fink M. Naloxone treatment of opiate dependence. *JAMA* 1971; 215:2108-2110.

[19] We tested increasing oral doses of naloxone up to 100 mg and intravenous doses to 10 mg for behavior and physiology effects in normal adult male volunteers. We saw no behavior effects nor any changes in EEG, so much so that I recorded my EEG and cardiovascular responses at 100 mg oral without measurable effect. Naloxone is an ideal therapeutic agent for a specific behavior effect.

[20] The study was undertaken by contract through the International Association for Psychiatric Research, a non-profit independent research foundation. The IAPR was incorporated in 1967, on the model of the Psychiatric Research Foundation of Missouri. A non-profit membership corporation, it was established to support research efforts in the work of Dr. Max Fink first at New York Medical College (1966-1973) and then at the State University of New York at Stony Brook. Both institutions recognized the service that IAPR performed in financially supporting the studies and in providing an independent monitoring Board for ethics of research in human subjects. The first grants were in support of the pharmaco-EEG studies of myself and Turan Itil. Until the project ended in 1975, the NIMH supported pharmaco-EEG studies first at New York Medical College then at SUNY at Stony Brook. This work was also supported by pharmaceutical industry grants-in-aid.
A 1979 NIH contract (HSM 42-70-98) supported studies comparing the effects of Greek hashish and US grown cannabis (marijuana) in Greek and New York users. Concurrent support for the studies at the New York Medical College was provided by NIMH contract 18172.

[21] The studies were done by members of Dr. Stefanis' University Department staff using the facilities of the Department and of Eginition Hospital. The New York members came from the staff of the New York Medical College.

[22] The experience was reported in numerous articles published in the academic press and presented at a conference. Dornbush R, Freedman AM, Fink M (Eds): *Chronic Cannabis Use*. *New York Academy of SciencesANYAA9* 1976: 282:1-430.

Chapters were also published in books edited by Monica Braude and Stephen Szara: *Pharmacology of Marihuana* NY: Raven Press, 1976) and M.F. Lewis: *Current Research in Marihuana* (NY: Academic Press, 1972) .

A summary of our Greek study experience was published in Stefanis C, Dornbush R, Fink M (Eds): *Hashish: Studies of Long Term Use* (NY: Raven Press, 1977).

[23] Drs. Costas Stefanis, Aris Liakos, John Boulougouris, Demitra Madianou, and C.P. Panayiotopoulos from Athens, Drs. Rhea Dornbush, Jan Volavka and Max Fink from New York.

[24] We also tested pure samples of THC-Δ-9 and various cannabis chemical constituents (THC-Δ-8, cannabidiol) obtained from Raphael Mechoulam of the Hadassah Hospital in Jerusalem. The samples were limited and we could offer no conclusions as to their activity.

[25]Rubin V, Comitas L. *Ganja in Jamaica*. Paris: Mouton & Co., 1975.

[26]Carter WE. *Cannabis in Costa Rica*. Philadelphia: Institute for the Study of Human Issues. 1980.

[27] Indian Hemp Drugs Commission. *Marijuana.* Silver Spring, Maryland: Thos Jefferson Publishing Company, 1969;

Mayor LaGuardia's Committee on Marihuana. *The Marihuana Problem in the City of New York*. Metuchen NJ: Scarecrow Reprint Corporation, 1973.

[28] My communications with Prof Mechoulam are digitized and available at the Max Fink Archives at the Stony Brook University Library Special Collections.

10 The Science of Quantitative Pharmaco-EEG

[1]Fink M, Shaw R, Gross G, and Coleman FS. Comparative study of chlorpromazine and insulin coma in the therapy of psychosis. *J. Amer. Med. Ass.*, 166: 1846-1850.

[2] Walter WG. An automatic low frequency analyzer. *Elec Eng* 1943; 7:203-19

[3] Ulett GA, Loeffel RG. A new resonator-integrator unit for the automatic brain wave analyser. *EEG Clin Neurophysiol* 1953;5(1): 113-5.

[4] Ulett GA, Johnson MW. Effect of atropine and scopolamine upon electroencephalographic changes induced by electro-convulsive therapy. *EEG Clin Neurophysiol* 1957; 9(2):217-24. He had built the device from imported UK excessed parts.

[5] Fink M. Quantitative EEG in human psychopharmacology: Drug patterns. In: GH Glaser (Ed): *EEG & Behavior*. NY: Basic Books, 1963, Chap 7: 177-197.

[6] Based on Ulett's report and his promise to build an analyzer I applied to NIMH for a supplementary grant of $10,000. Ulett's frequency analyzer was delivered to Hillside Hospital in the fall of 1958.

[7] Lincoln TX-O, 65,000 words of memory and 6 micro-second per memory cycle. Using recorded EEG played through an Analog-to-Digital converter with the words stored in the memory for statistical processing.

[8] Farley BG. Recognition of patterns in the EEG. In: MA Brazier (Ed.): *Computer Techniques in EEG Analysis. EEG Clin Neurophysiol* Suppl 20; 49-55, 1961.

[9] The programs and their logic were compiled in "Quantitative Analysis of the Electroencephalogram by Digital Computer Methods" by DonaldShapiro and Max Fink in collaboration with Connie Hickman BSEE and Turan Itil M.D. Copies are in the Max Fink Archives at Stony Brook University.

[10] Irwin, P. and Fink M. An empirical comparison of three EEG digital conversion techniques: baseline cross analysis, power spectral density analysis and Hjorth analysis. In: *Quantitative Analysis of the EEG*, M. Matejcek and G. K. Schenk (Eds.), AEG Telefunken, Konstanz, West Germany, pp. 379-393, 1976.

[11] We sought to establish a single overall measure of change in the EEG to assess the drug effect without inflating statistical probability by testing the multiple interdependent variables that these quantification algorithms generated. Irwin, P. Spectral difference index: a single EEG measure of drug effect. *Electroenceph. clin. Neurophysiol*. 54:342-346, 1982.

[12] Decades later Povl Munk-Jorgensen, the editor of the *Acta Psychiatrica Scandinavica*, invited psychopharmacologists who had been active in the early years to describe how thay had become interested in the new drugs. I chose to describe the pharmaco-EEG and computer applications in the essay "Remembering the lost neuroscience of pharmaco-EEG."*Acta psychiatr Scandinavica* 2010; 121:161-173.

[13] Fink M. Cholinergic aspects of convulsive therapy. *J. Nerv. Ment. Dis.,* 142: 475-484.
[14] We assisted Pfizer in setting up a laboratory in the state prison in Groton CT. Public pressure that such volunteers were not "free" and their study was considered unethical forced closure of the program within a year.

[15] The same model was actively developed by Turan Itil in St. Louis and then New York using the same drugs as standards. His students Bernd Saletu (Vienna), Werner Herrmann (Berlin), and Masami Saito (Osaka) developed similar services using his criteria.

[16] thiothixene, butaperazine, fluphenazine, fluphenazine decanoate, clozapine, thioridazine.

[17] chlordiazepoxide, triflubazam, bromazepam, brontizalam, fenfluramine.

[18] diphenhydramine, salicylic acid (aspirin), phenytoin, clonidine.

[19] Sulthiame, trifluperidol, tybamate, d-cycloserine, terfenadine, pirenzapine, fenmetazole, GP-41299.

[20]Theodor "Jack" Vossenaar was trained in medicine in Utrecht during WW II. He served as a translator for Canadian troops and then specialized in pathology, joining the Utrecht medical faculty. In 1971 he joined Organon and moved to become Medical Director of International Affairs. Two Organon clinicians, Peter Fell and Derek Quantock visited me at New York and encouraged Vossenaar to support EEG trials of mianserin. The success of this assay with resulting financial success for the company led to pharmaco-EEG trials of Organon products, the testing of 6-azamianserin and its isomers, various peptides produced by the laboratories by David de Wied in Utrecht, and the support of a testing center in Oss with chimpanzees under Henk van Riezen. Animals were housed and electrodes inserted successfully. Preliminary trials with test substances showed good recordings. But soon infection and death of some subjects ended the trials.

[21] I monitored 3 clinical trials of mianserin in the US finding that the contractors did not assess the clinical effects successfully, and Organon was unable to meet FDA standards for marketing. As the company had a similar agent, 6-azamianserin (mirtazapine) in clinical trials, they did not repeat the testing and eventually marketed mirtazapine in the US.

[22] I reviewed the mianserin pharmacology with Roger Pinder and lectured to invited groups of practitioners in Ireland, UK, Canada and US. This was my principal experience as a "Known-Opinion-Leader" for industry.
Pinder R, Fink M. Mianserin. In H. Lehmann (ed.): *Non-MAOI and Non-Tricyclic Antidepressants*. S. Karger, Basel. *Mod. Probl. Pharmacopsychiat*. 18: 70-101.

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11 The Road to Catatonia

[1] Faculty wore long white coats at the time, denoting their more responsible status. In the past half century, such traditions, indeed the wearing of clothes denoting status, have fadedm and identification of patients and professionals difficult.

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[4] Fink M, Taylor MA. *Catatonia: A Clinician's Guide to Diagnosis and Treatment*. Cambridge UK: Cambridge University Press, 2003.

[5] Today, we would have induced treatments daily and resolved the syndrome more rapidly. Fink M. Delirious mania. *Bipolar Disorders* 1999; 1: 54-60.

[6] Fricchione GL, Cassem NH, Hooberman D, Hobson D. Intravenous lorazepam in neuroleptic-induced catatonia. *J Clin Psychopharm* 1983; 3: 338-342.

[7] I interested the medical historian Edward Shorter in writing this history and by March 2017 we had written *The Madness of Fear: A History of Catatonia* that was under review for publication at Oxford University Press.

[8]Kahlbaum KL. 1874. *Die Katatonie oder das Spannungsirresein: eine klinische form psychischer Krankheit*. Berlin: Verlag August Hirshwald;
Kahlbaum KL. *Catatonia*. Translated by G. Mora. Baltimore: Johns Hopkins Press, 1973.

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[13] Organized by the Swiss Neuropsychiatric Society, Max Müller in Münsingen, Switzerland in 1937. Schweizerische Gesellschaft der Psychiatrie. *Die Therapie der Schizophrenie: Insulinschock, Cardiozol, Dauerschlaf*. *Arch Neurol Psychiatr* 39:1-238, 1937.

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Gelenberg AJ. Catatonic reactions to high-potency neuroleptic drugs. *Arch Gen Psychiatry* 1977; 34:947-50.
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relaxant dantrolene was recommended. For the next two decades, this concept dominated diagnosis and treatment of NMS until the connection to catatonia was widely accepted.

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Fink M. Lethal catatonia, neuroleptic malignant syndrome, and catatonia: A spectrum of disorders. Reply. *J clin Psychopharmacol*. 1997; 17: 237;
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[33]<www.nmsis.org.> An NMS internet hotline was created with acknowledged scholars responding to queries. For more than a decade the responders advised discontinuing neuroleptic treatment, prescribing dopamine agonists (bromocriptine, apomorphine) and dantrolene for the relief of muscle rigidity.

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Fink M. ECT in the management of delirium, NMS, and catatonia. *Essential Psychopharmacology* 2000; 3: 1-16.

[48] Jonathan Stanley, a wealthy donor supporting psychiatric research through the Stanley Foundation suffered an acute episode of delirious mania as a college student. Eventually he responded to medications with the diagnosis of "bipolar disorder." The failure to recognize delirious mania that must have carried the signs of catatonia became the basis for investment in bipolar disorder research rather than catatonia. See *NYTimes* story by Carl Zimmer and Benedict Carey, <http://www.nytimes.com/2014/07/22/science//

[49]Francisco Appiani has found a case of royal delirious mania in the 14th Century. During a very hot summer war campaign in Brittany, fearful of enemy attack, King Charles VI of Valois suddenly went berserk and attacked and killed four of his soldiers. When controlled, he was febrile, mute, staring, immobile, fluctuating in and out of frenzy and stupor. He gradually recovered. Appiani F. Delirious mania of Charles VI of France in the Fourteenth Century. *Acta Psychiatr Scand* 2015;132:499-500.

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[63] Kung DH, Qiu C, Kass JS. Psychiatric manifestations of anti-NMDA receptor encephalitis in a man without tumor. *Psychosomatics* 2011; 52:82-85.

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[83]Awareness of the history led the chairman of the McLean Hospitsal in Belmont MA, Dost Ongur to invite me to present the history to his staff on March 30, 2018. I was shepherded to the event by the Stony Brook University psychiatry resident Charles Mormando. It was an exhilarating experience, four years after my last prior public lecture.

11 Epilogue

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