Seventy Years an Experimentalist in Neurology and Psychiatry

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First Publication in Archives: May 28, 2017
Updated April 18, 2021

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Metrics: April 18, 2021
Pages: 100
Words: 38,107

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

Introduction

Inducing seizures to relieve severe behavior disorders-- electroshock, ECT -- is a much prejudiced treatment that is undergoing a renaissance after eight decades of experience. Usage is increased to varying degrees worldwide. But raucous attacks by public critics and psychologists claiming treatments cause brain damage and memory losses are ever common. But assured safety and remarkable efficacy, even guides to specificity in illnesses, brings the intervention within a successful medical tent. Introduced for the relief of the imagined Kraepelinian diagnosis of schizophrenia, recent decades has defined catatonia (and its varieties of mutisms, manias, motor rigidities) and melancholia (depressive psychoses) as more specific systemic disorders that are rapidly and effectively relieved.

How was the treatment discovered? And why was it rejected by the professions? Why the public stigma in the face of efficacy and specificity? How has the practice and the science of the treatment evolved?

The author, well on his way for full training in conventional neurology and psychiatry is asked to oversee the seizure therapies in hospitalized severely psychiatric ill. He takes on the task of improving the science and increasing public and professional acceptance are highlighted in this personal story of an experimentalist physician.

These pages cite my education as a physician with qualifications in neurology, psychiatry and psychoanalysis. From the beginning, I studied patients, their physiology and symptoms, and applied different interventions, often in a Random Controlled Trial. When I entered the profession, research studies in man was an accepted practice. In recent decades, bars to such studies have been increasingly applied, leading to focus on studies in animals and other surrogates. Over my professional career my interests focused on the treatment of induced seizures (electroshock, ECT), the effects of substances that altered brain functions (psychopharmacology, EEG), and the systemic behavior syndromes of catatonia and melancholia. The records of my studies are archived at the Stony Brook University Library. [1]

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Book One: Inducing Seizures as Treatments

My academic arc in electroconvulsive therapy began unexpectedly on January 2, 1952 as I enrolled for the fifth year of residency training in neurology and psychiatry at a hospital reputed to use classic psychoanalytic principles to treat hospitalized severely ill. I arrived on a clear winter day with another new recruit, to meet the Directors of this 170-bed multi-building Hillside Hospital caring for voluntary psychiatric in-patients, for up to a year, mainly at public cost.

That morning I was assigned to the electroshock and insulin coma treatment services. In my previous years, I had no experience with either treatment.

I received my M.D. degree from New York University School of Medicine on June 12, 1945, followed by nine-month interneship and 20 months service in the US Army Medical Corps. During the succeeding four years I studied in neurology and psychiatry residencies, attended a school of psychoanalysis, and sought a final year in psychoanalytic psychotherapy at an inpatient hospital in the Long Island farmland, with accredited training psychoanalysts on its faculty.

I accompanied the Associate Medical director to a 2-story building that housed the electroconvulsive (ECT) treatment unit. One by one, five patients lying on a wheeled stretcher under sheet restraints were brought into a treatment room, a rubber bite-bloc placed between their teeth, two stimulating electrodes applied at the temples, protected by two aides, 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 electric 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 light blue lips. After a minute, the muscles relaxed, deep breathing followed, cyanosis waned, and color returned as the patient was moved to a recovery room, cared for by aides for 15 to 20 minutes until able to get off the stretcher 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 injections of 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. Much was made of the newly developed anticonvulsant phenytoin (Dilantin).

And now, we were 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 in behavior accrue to repeated induced seizures in severely depressed, manic, catatonic, delirious, and psychotic patients. As I learned how to treat patients safely I realized the remarkable benefits of inducing seizures, and such treatments became an interest for the remainder of my professional life.

After introduction to ECT that first morning, we crossed the hall to the insulin coma treatment unit, a well-lit air-conditioned suite with a large nursing staff. Filled with cries, coughs, grunts, and groans of patients in various stages of stupor, coma, drowsiness and confusion, 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 or intravenously with measured doses of insulin. For the next three to five hours they were repeatedly tested for vigilance and response to commands as they lost consciousness; their tendon and pupillary reflexes disappeared, breathing became stertorous, and intense sweating soaked the bedsheets. After a measured hour, the 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. During 1/5 of the ICT treatments, at least one unscheduled seizure emergency occurred each morning. For the patients who had shown little change in behavior during the course of insulin comas, seizures were 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.

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 a state of *persistent coma* occasionally 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 stuporous coma during the six years that I managed the service.

By early afternoon, the ICT and ECT treated patients were in individual and group treatment sessions, participating in occupational activities, playing musical instruments and games, and meeting with relatives. I frequently tested their skills in chess and checkers, finding the skills of many better than my own despite their morning seizure or coma. It was remarkable to see a patient in coma, unresponsive

to verbal, sensory, or painful stimulation and an hour later chatting with staff, drawing, and playing games. Older patients, though, were more often confused and fatigued, spending a good part of their post-treatment day in their rooms or their beds.

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

By mid-year I had learned that ECT effectively reduced suicide thoughts, relieved negativism, aggression, depressed and manic moods. 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, other patients, and staff. 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 Creedmoor 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 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. 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 trials of psychotherapy before assignment for ECT or ICT. [2]

The teachers used 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 participants in 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.

Ending Insulin Coma Therapy

The introduction of Largactil (chlorpromazine) to Hillside Hospital in the fall of 1954 set in motion the demise of insulin coma therapy. Developed in France as a sedative, to reduce excitement and psychosis of the psychiatric ill, it first underwent safety and efficacy trials at various New York State hospitals. 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 and supervised by the ECT/ICT physicians. For the first trials we selected the most disturbed and least cooperative patients in one study unit. Patients became more responsive, less aggressive, less manic, and more cooperative. Soon, nurses from other units asked to enroll their patients. Initial reluctant staff attitudes changed quickly and our enthusiasm for chlorpromazine added to the voices encouraging its use from France and Canada.

But soon one patient and then another developed jaundice. Other study 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 was 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.

These motor signs were the fore-runners of the Parkinsonism and tardive dyskinesia that are hallmarks of chronic chlorpromazine use. Similar motor effects were soon reported for successor 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 ambulatory out-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.

The EEG profile of chlorpromazine 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 broad range of behaviors.

The 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, 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— clearly favoring chlorpromazine as a replacement for ICT. More than half of each sample improved sufficiently to return to their homes.[3]

These findings led to the closing of the Hillside Hospital's insulin coma unit in 1958, followed swiftly by the closing of 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.[4]

The treatment also persisted for decades in Russia and China, and was brought to Israel by Russian emigres. 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 random seizures were the basis for ICT's reported efficacy in relieving psychosis. ICT, to the extent it had therapeutic value, was best considered a less efficient and more riskful form of induced seizure therapy. [5]

Optimizing ECT Procedures

The EEG as Index of Seizure Efficacy

Since seizures were the core process in both ECT and ICT how can one record and understand the brain events that were central to the treatments? The answer seemed to lie in electroencephalography, but such was not available at the hospital.

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. Similar reports by Giovanni Aldini and Benjamin Franklin strengthened the conviction of electricity in living tissues.[6]

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 adapted the device that was developed to record the electrical activity of the heart to record electric oscillations from electrodes on the intact human scalp. Rhythms varied with changes in vigilance, sleep, body physiology, and the effects of systemic drugs. In his third report 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.

Hillside Hospital lacked an EEG laboratory. I sought training in recording and interpreting the EEG at the Mount Sinai Hospital in New York City supported by a fellowship of the National Foundation for Infantile Paralysis.[7] By the end of 1953 an EEG technician had been trained, a laboratory established, and developed a protocol for the study of the changes in EEG associated with ECT. An application to the National Institute of Mental Health funded a five-year study under Grant MH-927 "*Altered Brain Function Following Electroshock*" in the summer of 1954. The support established a team of researchers to study the treatments. For the next

decade, the physicians, psychologists, and technical staff were centered in a Department of Experimental Psychiatry.[8]

The EEG brain rhythms in alert normal adults are filled with 8-to-12 Hz (*alpha*) frequencies 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. 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 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. [9] But we could examine the "interseizure" record, the changes in the resting EEG record on days between treatments.

Brain electrical rhythms slowed and amplitudes increased during the ECT course. After treatment ends, more rhythmic, regularized alpha frequencies return. The changes induced 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.

We concluded that progressive slowing of inter-seizure frequencies was necessary for beneficial behavior effects. The patients whose inter-treatment rhythms changed very little did not recover from their illness. [10]

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. By comparing numbers of treatments and degree of slowing for each patient, 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

of the brain changes that underlie behavioral improvement. The rate and amount of change varied with electrical dosing and the number and frequency of treatments. We concluded that EEG change was necessary for the clinical changes to take place and marked 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 with ECT were similar to those in epilepsy and after head trauma was often used to justify an anti-ECT prejudice voiced by the public, by patients, and by psychiatrists and psychologists encouraging beliefs that seizures "damaged the brain." We thought otherwise, concluding that the EEG changes induced by the seizures were necessary markers for the clinical benefits -- without persistent EEG slowing, recovery of illness did not occur.

The patients referred to hospital for ECT are very ill, unable to function at home or at work, sad and unhappy, expressing thoughts of suicide, strange ideation, and occasionally with aggressive manic behaviors.[11] Almost all have been treated by a cascade of medicines, psychotherapies, vacations, diets, and much else before the patient was exposed to electroshock, widely conceived as hazardous and life threatening. The patients met today's diagnostic criteria for major depression, bipolar disorder, and schizophrenia. The quickest resolutions of illness occurred in the severely depressed, suicidal, catatonic, manic, melancholic, and delirious patients. The least benefits, 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. [12]

Modifying Seizures: Muscle Relaxants and Sedatives

Electroshock treatments were "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? What is it? [13]

Fractures of teeth, vertebrae, and long bones were unfortunately common. Many forms of physical restraint and chemical inhibition were tested. Curare, extracted from South American plants, prevented both the tonic (increased muscular tone, stiffening of the body muscles) and the clonic movements (rhythmic

movements of the stiffened musces) of the seizure.[14] But curare was unstable. In some patients curare effectively blocked the motor movements and in others, 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 ventilate 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 cost of the treatments.

In the spring of 1953 a new synthetic muscle relaxant suxamethonium chloride (succinylcholine) was introduced. Limb paralysis occurred within 30 to 60 seconds of intravenous injection, dissipating within a few minutes of its application, making it an ideal agent for ECT. In our first experience 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 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 by a nurse.

"Modified ECT" raised questions. 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 "anesthesia" became the province of organized anesthesiologists, psychiatrists administering a sedative and the muscle relaxant were no longer tolerated, effectively ending ECT in independent psychiatrists' office settings.

New sedation agents were studied. Benzodiazepines raised seizure thresholds, reducing treatment efficacy and outcomes. Methohexital offered short duration of action, safety and efficacy. 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 in onset and injection sites often became inflamed. Intramuscular ketamine usefully sedated 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, as in India, 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.[15]

Are Subconvulsive Treatments Effective?

Were the benefits of electroshock and insulin coma inherent in the changes in physiology associated with seizures and coma or responses 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 "sham treatments."

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.[16] 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.

The results of our study were published in my 1979 textbook *Convulsive Therapy.* That year the British psychologist Timothy Crow challenged the profession to prove the need for the seizure. His challenge elicited multiple UK government supported studies presented in an all-UK conference in September 1979 in Leicester, and in a published appraisal edited by Robert L. Palmer. No study supported efficacy of non-convulsive treatments, reconfirming the critical role of the induced seizure.[17]

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 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 breaths elicit a full grand mal seizure, usually within a few minutes.

Four research teams – Joyce and Iver Small at University of Indiana, Albert Kurland at the Maryland Psychiatric Center, Björn Laurell in Sweden, and I and my associates at Hillside Hospital 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 study, 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 in the treatment room were deterrents. The smell was unpleasant, objected to by both patients and staff members. 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.[18]

Decades later, the pre-occupation with memory loss led to widespread reduction in treatment efficacy because many practitioners shifted to unilateral electrode placement, ultra-brief currents, and minimal dosing. Increasing reports of treatment failures sent me to re-assess the experience with flurothyl as a potential non-electricity seizure induction method. In the first quarter of the 21st Century, when repeated hospital site procedures for renal dialysis and chemotherapies and radiation for cancers are widely accepted, 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. [19] Alas, I failed to entice any clinician to undertake such reassessment.

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. Isoflurane is an inhalant anesthetic that quickly induces stupor, inhibition of EEG rhythms, and a flat-line EEG. 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 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. Isoflurane EEG suppression was deemed not an effective alternative for the seizures of ECT.[20] Periodically, this technology prompts interest and is re-evaluated. The studies have been poorly controlled and the reports convey authors' enthusiasm without evidence of persisting behavioral or physiologic effects.

Role of Acetylcholine: 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 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 reported that anticholinergic atropine and atropine-like drugs blocked both post-seizure EEG slowing and the anticipated behavioral recovery after ECT. Herman Denber reported that injections of the chemical diethazine, another anticholinergic agent, reduced EEG slow wave activity after ECT. We replicated the finding for diethazine and also found that the antiparkinson agent procyclidine and various experimental anticholinergic drugs known as the JB-series also 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 EEG 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. We concluded that 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.

Free acetylcholine and acetylcholinesterases were elevated in the cerebrospinal fluid (CSF) of epileptic patients. CSF acetylcholine levels increased during ECT. In cats subjected to graduated head trauma, the amount of free acetylcholine and cholinesterases in the CSF increased with the severity of the trauma.

I imagined that induced seizures, like cerebral trauma and epileptic seizures, altered cerebral permeability, increased free acetylcholine and cholinesterase levels in the brain, slowed EEG frequencies and increased amplitudes and rhythmic bursts. I pictured these biochemical changes as the basis for the behavioral effects we were seeing with ECT.[21]

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, that were then 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.

Neuropsychological Tests and EEG Slowing

Immediately after a seizure, the patient awakens in confusion, poorly oriented as to location, date, or month, and often 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 vary with the number and frequency of seizures, the sedative and electricity doses, but most important is patient age -- elderly patients are confused longer. With recovery to mental health, 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.

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 was more often scored in older patients, in the less well-educated, and in immigrants with English as their second language. Scores on the Rorschach test were loosely correlated with the treatment outcomes but the specificity and predictability of the Rorschach criteria was low. 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. The patients with high authoritarianism scores were more likely to show benefits from ECT.[22]

Book Two: After an ECT Research Hiatus, Renewed studies

During a 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 our studies. 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 ARNMD in New York City. He had compared the clinical benefits and changes 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. 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 developers of *electroconvulsive* therapy. He had published a leading textbook on the somatic therapies in 1946. 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: What is the optimal placement of electrodes in inducing seizures? We randomized patients to seizures induced either with non-dominant unilateral or with bitemporal electrode placements, measuring clinical, cognitive, and EEG changes at weekly intervals. And, 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.

The Differences Electrode Placement Makes, Again [23]

We tested 76 patients with a mean age of 63.4 years, 43 treated with bilateral and 33 with unilateral placements. By diagnosis, 60 patients were endogenous depressed and 16 reactive (neurotic) depressed. 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.

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 memory tests during the treatment course changed less in the unilateral treated patients than the bilateral, varying with the task selected. 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. [24]

EEG frequency slowing was greater after bilateral placement than after unilateral. An asymmetry was also observed in EEG slowing, accentuated on the right side with right unilateral electrode placement, and on the left side in bitemporal-treated patients. 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. [25]

Can Multiple ECT Treatments Per Session (MMECT) 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 single treatments. Post-ictal sleep among the MMECT patients was prolonged with greater disorientation and clouding of consciousness especially among the older patients. Neither we nor the experienced clinicians whose patients we treated were convinced that multiple treatments in a single session were an effective modification.

We confirmed 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, experienced 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.

ECT in Systemic Medical Illnesses.

In 1972 I accepted an appointment at the Stony Brook Medical School to teach psychopharmacology and develop an ECT Service at University Hospital. As 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, cardiac pacemakers, malignant catatonia, anemia, Parkinsonism, delirium, and pseudodementia.

ECT in Adolescents. 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.

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. A 14-yr-old mentally retarded boy with persistent self-injurious behavior (SIB), unresponsive to social and medication treatments was referred for treatment. He was admitted wearing helmet, glove, and camisole restraints to keep him from injuring his head, monitored by full-time aides for continuing protection. 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, Director of the Neurobehavioral Unit of the Kennedy Krieger Institute of Johns Hopkins University, would identify SIB as a form of catatonia in autism, relieved by ECT.[26]

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. 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 labelled "pseudodementia." Both the mood disorder and the dementia signs disappear with effective antidepressant treatments. All patients admitted to my psychiatric ward suffering "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 was 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.[27]

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.

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, we successfully treated deliria in post-surgical patients, those with abnormal systemic hormonal and fluid balances, and in alcohol withdrawal. 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 ECT in 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. But the CSF pressures do not rise during our modified treatments. We reported safe treatment in a patient with a growing meningioma and in another patient with a large arteriovenous malformation.[28] 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.[29]

Optimizing Treatments.

Anesthetics. After the hiatus from the ECT studies at Hillside Hospital in the 1950s, we again evaluated 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 again found a special use for ketamine in delirious patients – an intramuscular injection sedated 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.

Seizure durations. 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. 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.

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.

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 in their syndromes. 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. I was invited to write several reviews on the role of ECT in schizophrenia, each time offering ambivalent opinions in the report.[30] 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.

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 described later, this form was erroneously identified as schizophrenia, and is best appreciated as a uniquely identifiable, verifiable and treatable disorder.

The presence of mood disorder in conjunction with schizophrenia confuses 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,

catatonia and melancholia, all other 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, including the DSM-5 of 2013 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, illness course, and family associations. 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.[31]

Clozapine and ECT. A patient's slow responses to chlorpromazine or fluphenazine is often augmented by concurrent 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 serum clozapine levels 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.

Such combined treatments was encouraged , however, 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.

The faculty at Hillside Hospital had supported clozapine use in therapy-resistant psychotic patients. Many patients, 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 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. [32]

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? 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. We measured the brain concentrations of fluphenazine in rats treated with electroconvulsive shock but were unable to record a difference.[33]

The CORE Study of ECT in Depressed Inpatients.

In 1992 the psychologist 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 (using unilateral electrode placements) 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. 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 the Columbia University Consortium study. The single distinction was the CORE use of bilateral electrode placements at a minimum of 1.5 times the measured seizure threshold while the Columbia group used unilateral electrode placements with dosing set at 1.5 to 2.5 times the measured seizure threshold in their treatments.

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, although 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. [34]

In Columbia'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.

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.) [35]

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

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 60% with six treatments within two weeks, justifying ECT as the primary treatment in patients who require special protections for suicide risk.

Delusions in depressed patients identify a population of ECT-responsive patients. In the 1970s, Alexander Glassman and his colleagues at Columbia University reported that delusional depression did not respond to blood-level, monitored imipramine treatment. They did respond to ECT, however. 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 in its efficacy and its ethics.

The Persisting Stigma: Memory Loss and ECT

The argument that memory loss is a critical risk in all induced seizure treatments persists, however, encouraged by the constant singing of a "memory loss" mantra by psychologists and by some in the laity. 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 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. [36] Physicians are applying unilateral electrode placements knowingly offering patients lesser effective treatments that increase risks of treatment failure and higher relapse rates.

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, weight loss, 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. 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 disoriented. They are then given a chemical intravenously that puts them to sleep, electrodes are pasted on the 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 toxins – every "psychoactive" pill, whether antidepressant, anxiolytic, or neuroleptic or whether the alcohols, marijuanas, opioids or sedatives that are publicly attractive -- 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?

And on, and on.

When tests are repeated after many hours, the answers are slow but 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-altered by an extensive potpourri of medicines.

When specific neuropsychological tests are presented 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, often better than during the illness. In batteries of more than 20 tests, psychologists have generally found that the normal functions have returned with only personal memories still offering errors. Of course, psychologists have prominently carried the "memory loss, memory loss" mantra against ECT by attention to these singular test data, not relating their test measures to the clinical changes and benefits 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 themselves. For the many who recover, these deficits disappear, and they 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 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 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 sponsoring industrial companies) thrives on the falsehood that these treatments "do not affect memory."

My personal experience lead me to conclude that 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 Richard Abrams' textbook.[37]

Book Three: Electroshock in the Public Eye

Creation of Induced Seizures as Therapy

Was the mark of Cain that prejudices the use of inducing seizures to relieve emotional illnesses deserved? The carnage of the First World War released inhuman 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. Skills in neurosurgery encouraged open brain surgery and electrode placement and stimulation by deep brain stimulation, leaving many with permanent brain lesions. Although electroshock had none of these risks, it was lumped together since the practitioners of one were called upon for all.

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 panic induced by a partial seizure. Despite panic and pain, the occasional fracture, the immediate confusion, the relief occasioned by many of the first patients encouraged its continued use. In his review of his experience, Meduna reported half his patients improved sufficiently to leave the hospital.[38]

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 become the principal 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. 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. 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.

ECT Immediately Rejected By the Profession

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. 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 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. In the 1970s romanticizing Freud became fashionable for Hollywood and Broadway, 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.

The 1973 review of practices in Massachusetts did find hospitals where ECT use was excessive, seizure inductions haphazard, and medical care facilities inadequate. Greenblatt issued medical guidelines to standardize ECT practice. His report and the regulations satisfied both 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 ECT were active. 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.[39]

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 accepted medical practice. The court agreed that the 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. These regulations are still in effect in 2021 and severely limit ECT use, especially in adolescents. The same restrictions were adopted in Texas in 1993 and in other states to a lesser degree.

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. 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.

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.

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. 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 morbidity. 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 with the bilateral), to support the practices and beliefs of some members.

How best to assure consent? Patients referred for ECT are severely 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, and properly witnessed. The form would name the treating 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 agreed before submission to the APA.

ECT was viewed as a surgical procedure (since it uses anesthesia) with a potential for harm that must be specifically 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. These were considered to be the family and community responsibility. State-mandated procedures for judicial authorization for treatment on an incompetent patient's behalf were supported by the task force.

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 written 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. The 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.

Out-Patient ECT: Association for Convulsive Therapy Commission

Post-World War II, ECT patients had been increasingly treated as outpatients in doctor's offices, both for their treatment courses and continuation treatments. But as ECT in the 1980s 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 early office practitioners and those treating patients at Gracie Square Hospital. 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 consent, was widely accepted as recommended by the ECT Task Force of the American Psychiatric Association in its 1978 report. 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 clinicians 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. 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. [40]

The Stigma Persists: The Public Joins the Attack

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 and psychologists' 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. She instituted a malpractice suit against the psychiatrist who administered the treatments complaining that she had not been warned that her memory would be affected and that she would be unable to work.[41] 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. (The Court supported the physician defendant.)

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. 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.

Church of Scientology and Malpractice Legal Suits

In the 1960s, the national political and social movement of Scientology led 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. She had been given ECT as an outpatient with 13 treatments in 19 days. The physician deemed the patient suicidal, but failed to offer her hospital protection. She complained that her memory was so damaged that she could no longer work. While I did not believe that the patient had suffered compensible 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.

Media Attacks: 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.

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 arranged 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:

'*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 psychiatrist, as the basis for his negative attitude to medicine. Whether this relationship contributed to his views of psychiatry or not, he was among many creative writers who saw psychotherapy and psychoanalysis favorably, indulged by themselves, friends and family members, seeing electroshock treatments as hazardous, ineffective, and not acceptable in their social class.

An Active Defense: 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 John Nash, the 1994 Nobelist in Economics. 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. 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.

I reviewed 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. 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. 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. I realized that the efficacy of insulin coma therapy lay in the occasional grand mal seizure, that ICT is best seen as an imperfect form of induced seizure therapy.[42]

Book Four: The Enigma: How Do Seizures Alter Behavior?

Seizures are Inherent Reflexes

Grand mal seizures are patterned reflexes 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 both 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 methods, and the electrical induction of seizures -- electroshock -- quickly became a widely accepted treatment of the 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. Attempts to treat patients by subconvulsive electric or magnetic currents or by non-seizure inducing anesthesia (isoflurane) dosing have been unsuccessful in eliciting behavioral benefits.

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." That construct was re-labeled the *neurophysiologic-adaptive* view a few years later. I argued that the changes in behavior, toward greater denial of illness, was facilitated by altered brain physiology.[43]

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 *cholinergic theory*. I argued that seizures increased the brain levels of acetylcholine and 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 transmitters 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. I sought to confirm these reports in our patients treated with ECT at the Northport Veterans Administration hospital in Eastern Long Island. When Jan-Otto Ottosson also saw merit in a neuroendocrine image of ECT, we formulated a *neuroendocrine theory* that we published in 1980.[44] After forty years, 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 behavior 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), 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 may be readily perceived but the perception of two simultaneous stimuli varies with the subject's alertness and vigilance. The errors are 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*.

During the course of electroshock, errors increased with numbers of treatments. The greater the degree of EEG change, the greater the perceptual errors. 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. 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.

I studied the expression of denial during ECT by weekly amobarbital and EEG tests and recording patient responses. 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. 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 daily activities. After treatment, the complaints are relieved and when asked what is wrong, they deny 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.[45] 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 blocked acetylcholine stimulation. The chemical was a new moiety created in industry with the hope that it might have clinically favorable psychoactive properties. He was unable to identify a clinical benefit, reporting that patients became more disorganized and irritable. I tested 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. 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. Similar reversal of mood was also reported after injections of the experimental anticholinergic JB-329 (Ditran) and its congeners, supporting the connection between brain cholinergic levels and mood.

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. CSF acetylcholine levels increased during ECT. In cats subjected to graduated head trauma, the amount of free acetylcholine and cholinesterases in the CSF increased with the severity of the trauma. Again, hubris allowed me to picture the physiologic consequences of induced seizures as similar to those of head trauma.[46]

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

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, that were then 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 Neuroendocrine 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.

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. 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.

Cortisol derived from the adrenal gland was a 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. 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.

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 confirmed the relationship between severity of depression, abnormal DST, and the response to ECT that Carroll had described. 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 into 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 same 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 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 forms of the illness.

In the 1980s I attempted a study of peptides in the cerebrospinal fluid during ECT. 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 ß-endorphin but a non-significant rise in somatostatin.[47]

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.

Conferring in the Search for the Mechanism

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 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*. Attention was focused at the meeting on the neurophysiology of seizures, the role of changes in cognition, and the neurochemistry of catecholamines.[48]

The panelists dedemed persistent changes in EEG recordings 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 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.*"

In the 49 years since that meeting, the ECT literature has been filled with correlations of brain and systemic increases of many biochemical and behavior measures. But no study has offered a consistent association between neurotransmitter functions and changes in mood and thought, either for induced seizures or for any of the many psychoactive pills.

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. 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. 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.

1985. The hostility and controversies about ECT encouraged the NIMH to hold a public Consensus Conference in October 1985. 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. 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. 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. The same hurdles were described by Pesach Lichtenberg and Bernard Lerer and by Sukdeb Mukherjee in discussing the relief of mania. 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. 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. 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. 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. Reviews by John Mann and Ron Duman were no more useful. Nor was an explanation based on the anticonvulsant actions of seizures. 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. The present editor of the *Journal of ECT*, Vaughn McCall organized another review of mechanisms. He asked Pascal Sienaert to organize the reports that were published in June 2014. 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.

Roger Haskett of the University of Pittsburgh discussed the neuroendocrine hypothesis. 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 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.

Book Five: The Road to Catatonia

During my days in medical school and residency training I assume I observed 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 and obtain the cooperation of the negativistic and the mute. 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 in 1980, when I became responsible for supervising the care of acutely ill patients and teaching students on the in-patient unit at University Hospital at Stony Brook. My experience with a fully restrained delirious woman and the resolution of her illness excited my interest..

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 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. 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.

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. 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 lorazepam treatment while studying at Boston's Massachusetts General Hospital, 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.

Catatonia as a Type of Schizophrenia

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*." 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, nine suffering from seizure disorders, three with neurosyphilis, and two with tuberculosis. 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.[49]

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.* 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 renamed 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.

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.

But Catatonia Is Not Schizophrenia

Awareness that catatonia was not limited to patients with schizophrenia came slowly. 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. 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 Alan 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. They reported the salutary effects of treatments and a factor analysis of the data identified two factors, one associated with mania and good outcome with treatment.

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. 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. He ascribed the syndrome to excessive dopamine blockade and prescribed dopamine agonists such as bromocriptine. In time we learned that these treatments were ineffective, and they were replaced by lorazepam and ECT, the effective catatonia treatments today.

In Contrast to Schizophrenia, Catatonia is Treatable.

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.

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 Lipótmezó 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. His method of induction was inefficient, however, 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. 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. Three years later he published his experience with 110 patients, reporting relief in more than half, especially among those acutely ill with catatonia.

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?"

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. 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.[50]

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°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.

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. 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. 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 the same psychopathology.

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. 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 malignant catatonia and treated with benzodiazepines and ECT. 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, as I viewed NMS as a form of malignant catatonia.

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. 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.[51]

Simultaneously, the neurologist Daniel Rogers from the Burden Neurological Hospital in Bristol, England presented a similar challenge. 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 encephalitis epidemic, indicating that catatonia was not confined to

schizophrenia. He described a systematic examination and a rating scale to identify catatonia, defining catatonia within neurology practice.[52]

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 illness classifications.

The Drive to Official Definition.

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.

Using that rating scale in 1994-95 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. 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 (DSM 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.

The Sedative Verification Test

Could the relief of catatonia's signs with intravenous lorazepam confirm the diagnosis? Since William Bleckwenn had rapidly resolved catatonia with injections of amobarbital, 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. 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 were widely adopted and central to the recommendations of the textbook of catatonia that Taylor and I published in 2003. [53]

The Many Faces of Catatonia.

Beginning with our recognition of NMS, Michael Taylor and I soon accepted 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 that were relieved by 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. 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.

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. 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 daily ECT was demonstrated in 1952 by Otto Arnold and H. Stepan. 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 .

The Stony Brook hospital unit consists of rooms around a circular core. From the entrance to the ward it is possible to see the doors 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.

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. 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.

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 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. 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 catatonia in severely manic and delirious patients and offering catatonia treatments is an unheralded aspect of the understanding of mania.

But delirious mania is still not recognized in the revised nomenclature of DSM-5 published in 2013. 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. [54] Michael Taylor makes the same observation in his personal history as researcher and clinician titled *Hippocrates Cried*.[55]

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. 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. 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." 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 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 apply proper tests.

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.

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" among Syrian refugees in Sweden and a "Nodding Syndrome" 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.

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. 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.

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. 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.

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. 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. These characteristics assure the syndrome's definition within the medical model. 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." 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 February 2021 increased to 1588 with 83 with catatonia, and 19 with the catatonia treated with ECT.

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 exhibit persistent repetitive movements, often screaming and 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. 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. A 2014 report describes an 18-year-old man with a 8-year history of progressively severe GTS that responded rapidly to ECT. 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 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.[56]

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). 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. 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. 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.

During these recent DSM deliberations the initial debates occurred between classical scholars represented by Gabor Ungvari 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 ECT. 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.

Publication of a Catatonia Textbook and an ACTA Supplement

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. At the same time we presented our experience in a review in the *American Journal of Psychiatry*.

We are 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, neurology, and psychology, 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*. 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.

How is catatonia best recognized and what is its place in the medical world? We soon came to see it as a behavior syndrome, severe and occasionally fatal but treatable, so much so that its resolution left no residual marks. Edward Shorter and I discussed these many aspects of the syndrome and in the fall of 2016 resolved to write its history. We organized our thoughts and decided that we could best assess the syndrome as an atavism, a relic of the primitive stages of animal development when fears encouraged defenses of freeze, flight, or fight. We formulated these thoughts in an essay asking "Does persisting fear sustain catatonia?" in the *Acta Psychiatrica Scandinavica* in 2017. [57]

A proposal for a volume by Shorter and myself was accepted by the Oxford University Press, and in July 2, 2018 the first copies of *A Madness of Fear: A History*

of Catatonia with the deep blue cover image of Caravaggio's *Medusa* were published. The text describes the 150 year story of a systemic medical syndrome, the successful application of the Hunterian model of the identification of a systemic illness. It joins neurosyphilis and melancholia as among the few behavior disorders that is identifiable, verifiable and successfully treatable.

Book Six: Melancholia and the Medical Model of Diagnosis

After publishing our text on Catatonia in 2003, MickeyTaylor and our wives Ellen and Martha met for a celebratory lunch in Chicago.

"Well, what is next?"

We agreed that Melancholia was a discussable syndrome -- multiple forms were widely recognized, each responsive to the tricyclic imipramine and to ECT, and a verification test in the dexamethasone suppression test had been described. Melancholia syndrome met our criteria for a medical diagnostic syndrome, parallel to our image of the catatonia syndrome, and we both had successfully treated melancholic patients. [58]

Like catatonia, melancholia is not recognized as a clinical entity in any of the American Psychiatric Association *Diagnostic and Statitical Manuals*, although it is widely described in the clinical literature. Melancholia is accepted as a descriptor or modifier for DSM diagnoses, not as a distinct identifiable entity, not accorded a specific code. As a consequence its study is not well defined, not recognized in the citation indices, and is poorly studied; it is buried in the Major Depressive Disorder and Bipolar Disorder categories. The parallel with the catatonia story is uncanny.[59]

During my Hillside Hospital experience, the treatment of severely depressed patients, suicidal, anorexic, insomniac, mute and stuporous, with ECT was remarkably effective. Often, inducing seizures daily resulted in complete relief in 2-4 days, with suicide risk, appetite, insomnia and withdrawal fully relieved. In our RCT study of chlorpromazine and imipramine, we identified a population of psychotic depressed patients that responded to both agents.[60]

In my days in Missouri, we often identified melancholic patients but their diagnosis and treatment was of no particular interest. In our studies of ECT at Gracie Square, the clinicians recommended psychotic depressed, postpartum and partum depressed for treatment without our particular attention to their identification.

The Dexamethasone Suppression Test*:* By the 1960s, chemists had reported serum cortisol measures to be elevated in melancholic patients. By 1972, the Australians Davies, Carroll and Mobray reported that a straighforward test, the Dexamethasone Suppression Test (DST) was a marker of severe psychotic depressive illness. Diurnal serum cortisol levels were elevated, and administration of the steroid dexamethasone failed to suppress the elevated levels. One report by Bernhard Carroll intrigued me. Five severely ill melancholic patients with abnormal DST responded clinically to courses of ECT; their DST normalized. Two relapsed, again with abnormal DST tests; re-treatment with ECT resulted in clinical improvement, again with normalization of the DST.[61] Was the DST a marker of melancholia and predictor of the response to ECT?

I had been asked to supervise a psychiatric unit at the Long Island Northport VA in 1972. I organized clinical trials of a potential psdychotropic drug flutroline, which we found clinically ineffective. In 1968, the Fellow supervising treatments Yiannis Papakostas, accepted the tasks of developing the chemical tests for cortisol and TSH testing patients before and during the course of ECT.[62] Of 20 unipolar melancholic patients, 16 exhibited abnormal DST. Of the 14 treated with ECT, all test normalized with recovery. These findings stimulated interest in cortisol as a test of a specific form of depressive illness.

Over the next few years, numerous reports associating the DST and depressive disorders, some finding a close association with severe depression and psychosis, others finding poor relations. The APA TAsk Force on Laboratory tests concluded that the test was not useful in identifying major depressive illness.[63] As I and Bernard Carroll noted, a laboratory test with high specificity for melancholic depression was applied to a broad class of "major depressive illness" that included neurotic and characterological depressions, those unhappy with their social status and lives. The patients with positive DST tests were the severely ill, often suicidal, unresponsive to psychological therapies, but responsive to the more effective antidepressant tricyclic medications and ECT. Never the less, the DST was rejected as a test of a specific form of depressive illness; each variation of the DSM (-III, IV, -5) discarded all laboratory tests for the diagnosis of any of its hundreds of described conditions.

Earlier I described my development of the CORE collaborative studies of depressed patients treated with bitemporal ECT with continuation treatments either lithium and nortriptyline or ECT. The study was an excellent opportunity to test the DST and severe depressive illness, but the NIMH committee and managers reviewing the study budget, rejected funding for the DST, justified by the APA Task Force report. Never the less, we examined the rating scales of our depressed patients for evidence of the *loss of pleasure in all, or almost all, activities* or *lack of reactivity to usually pleasant stimuli* at baseline. Of 489 patients in the CORE study, 311 (63.6%) met criteria for melancholic features. The overall remission rate was 68.1%, with higher rates (78.7%) for those who did not meet the melancholia specifier criteria and 62.1% of (or more) of six cited vegetative signs of melancholia. The specifier is added on the basis those with melancholia specifier (42). We concluded that the approximation of "melancholia" in our patients was a poor substitute for the DST.[64]

After our meeting in Chicago, a flurry of letters, interim reports, literature searches, led to our publication in the Spring 2006 by Cambridge University Press of our melancholia textbook.[65] We described the century-old experience, defined the syndrome by psychopathology and laboratory tests, treatments by medication and ECT, and argued for its recognition as a distinct entity in psychiatric classifications. The book was well presented but was priced very high, the advertising minimal, and the distribution disappointing.

Increasing interest in melancholia led to an international conference in Copenhagen of authors who had studied melancholia, also in 2006.[66] By the conference end, melancholia was defined as an identifiable mental illness, the DST was agreed as a defining test, and ECT as a definitive treatment. The argument for a unique identity among behavior illnesses was again made. Discussions with members of the DSM-5 panel for depressive illnesses were strongly made, but again ignored in DSM-5 in 2013.

Disappointed with our failure to convince clinicians about the unique qualities of melancholia, both Taylor, in his book *Hippocrates Cried*[67], and I, joining with Edward Shorter, described the story in *Endocrine Psychiatr* that we published in 2010.[68]

At this editing in March 2021, melancholia iremains buried among the diverse illnesses coded as major depression and bipolar depression. Like catatonia, the illness needs efforts to identify its biology, to bring it out of its burial, much as was successfully done for catatonia.

Book Seven: Studies in Electroencephalography (EEG)

EEG Introduced to Hillside Hospital 1953

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. Spontaneous seizures and the rhythms of the inter-seizure EEG in epilepsy were next described. 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 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, Long Island.)

With Hans Strauss and Mortimer Ostow 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. An application to NIMH funded a five-year study under Grant MH-927 "*Altered Brain Function Following Electroshock*" in the summer of 1954.

Hans Berger had recorded rhythmic frequencies of 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 Hannah Mosquera and I measured the height and width of each wave in 10-second epochs for 60 to 120 seconds in artifact-free samples for each weekly recording. We scored the records as *low, medium* and *high* degree changes. As the recordings were done weekly, we had six to eight records for each subject. Progressive slowing of frequencies and increased amplitudes marked treatment courses. In later records, bursts of slow waves with sharp spike activity were seen. The best clinical recoveries occurred 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 were "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 or Thursdays. These records showed varying degrees of progressive slowing with increasing numbers of treatments.

The grand mal seizure was the central feature for changes in behavior and the beneficial behavior effects. With increasing numbers of seizures the EEG rhythms slowed and the amplitudes increased. The patients whose inter-treatment rhythms changed very little did not recover from their illness. Those with greater degrees of slowing had the better clinical evaluations. The development of slow rhythms and higher amplitudes were markers associated with recovery.

Necessary, but not sufficient. Some patients with these rhythms did not show beneficial behavior changes. At the time, we were treating a wide range of illnesses. Many would meet criteria for major depression, bipolar disorder, and schizophrenia in modern classifications. The schizophrenic patients, except those with the catatonic form of the illness, showed the least benefit with 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 reported on the EEG effects of ECT and ICT; then the changes accompanying many new psychoactive drugs introduced after 1954. I developed methods to quantify EEG changes using digital computer methods; classified psychoactive drugs by their EEG characteristics; and developed and defended the contentious concept of the "*Association of EEG and behavior with psychoactive drugs in man*." [69]

EEG in Psychopharmacology

By 1954, the first clinical tests of chlorpromazine found it to be very effective in reducing aggression, excitement, and paranoid thoughts. The EEG profile of chlorpromazine differed from amobarbital and ECT. Imipramine (Tofranil, IMI), our next new agent, was also distinguishable from chlorpromazine. Were these differences related to their differing behavior effects? And how were the changes related to behavior changes?

While the changes in EEG during 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 an 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 degree of EEG slowing to assess the severity of head trauma. 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. 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 to measure the effects of atropine and scopolamine on the post-seizure EEG. 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.

I visited Ulett in St Louis and was impressed that the device did measure the drug-induced EEG changes. I received funding from NIMH and Ulett built a device for my studies at Hillside. 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. Ten seconds of analog electrical activity were digitized and then measured by two statistical programs labeled power spectral density and period analysis.

The Walter analyzer was inherently unstable and 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 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, we concluded that the baseline cross and power spectral analysis gave us the best measures of medication effects. Some years later, we compared the relative merits of these analysis methods, concluding that the methods offered useful analogous measurements.

IBM-1800 Analysis System*:* In 1966 I moved to New York Medical College to study opioids and their antagonists, hashish, and marijuana, and to renew my studies of ECT. Donald Shapiro joined me, and in 1967, with NIMH funding we leased an IBM-1800 computer system that he 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.

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 researchable and fundable questions. 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.

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, absorbed 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 EEG 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. In New York we studied new drugs in healthy male volunteers, paying for their hourly participation, and found such trials useful to identify the central effects of new entities.

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. 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.

Numerous world laboratories studied the EEG effects of psychoactive agents and with the leadership of the German scientists an International Pharmaco-EEG Society (IPEG) was formed and met every two years. The behavioral and

physiologic effects were defined in patient and volunteer trials. Many consulted with industry pharmacologists and offered identifications of clinical activity that was inconsistent with the predictions of drug effects in animal studies. While the human studies were more reliable and predictive of the clinical activity of the compounds, these were expensive, time consuming, and difficult to fund and carry out. The association of EEG and human behavior was discussed at the 1966 meeting of the CINP, in a symposium on "Anticholinergic Drugs and Brain Functions in Animals and Man." The dissociation between predictions of behavior effects in animals and man was not resolved.[70]

As new entities were created in industry laboratories increased emphasis on the absence of side effects resulted in compounds sent to the clinic with decreasing efficacy. These were identified as selective serotonin and norepinephrine reuptake inhibitors and the atypical antipsychotics. At clinical dosing and in volunteer trials, the impact on EEG were hardly measurable. We were unable to identify patterns the we had established for different behavioraltering agents. Our methodology was criticized as failed, and discarded. But over the past three decades, the benefits of these new agents were increasingly not distinguishable from placebo comparators. Not understanding the role of brain change measurable by EEG in man has resulted in a worldwide flood of ineffective medications.

Psychopharmacology Lessons Learned by Pharmaco-EEG

Over the three decades of activity, we profiled agents that were clinically active and some marketed, measured the relative potency and dosage ranges of sedative and stimulant drugs to guide clinical use, examined the psychoactive properties of agents in the search for a new useful chemical core, and agents that showed little promise that were abandoned. 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 had 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 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, 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. I became invested in the EEG-mianserin story and presented the findings in many venues.

Mirtazapine**,** 6-azamianserin. 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.

Aspirin, Anticonvulsants, Antihistamines*.* We looked at commonly marketed agents with reputed behavioral effects seeking potential alternative clinical uses in their EEG profiles. Acetylsalicylic acid (Aspirin) was 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 effects, and cognitive functions characteristic of soporifics. Doses of 0.65 Gm were similar in direction and pattern but failed tests of significance.

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.

In an enthusiasm for peptides following the identification of euphoriant effects of beta-endorphin, we examined the effects of the peptides $ACTH_{4\text{-}10}$ 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.

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

Opioids and Cannabis. The same principles of EEG study of new agents were applied to opioids and their antagonists, and hashish, marijuana 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 marijuana and hashish the behavior and EEG effects were consistent with THC-Δ-9 content.

The Association/Dissociation EEG and Behavior Controversy.

Industry searches for new agents with potential for human benefit are commonly based on similarities in chemical structure and observations 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, EEG 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.

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. In time the anticholinergic effects of imipramine were increasingly recognized. The anticholinergic properties were even flouted as riskful 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.

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 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. He concluded that there was a *dissociation between the induced behaviors and the EEG effects*. His inference was supported by pharmacologists studying 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 acknowledgement that the systemic and brain pharmacology of animals are not identical to that of man. 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 setter dogs 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 behaviors of psychosis, depression, or anxiety, elicit a delirium or reduce a manic episode, from the EEG changes. Failure to alter 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. [71]

Book Eight: A Medical Experimentalist is Created

Medical School Experiences 1942-1945

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 dressed as Privates First Class in the U.S. Army. The war had called many experienced faculty members to military duty offering 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 did medical research at 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 crossection models 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 and Cerebrospinal Fluid: 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 of active neurosyphilis. While at Vienna's Allgemeines Krankenhaus, 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 guides to treatment.

Withdrawal of cerebrospinal fluid by lumbar punctures between Lumbar- 3 and Lumbar-4 vertebrae are often followed by headache. To reduce this incidence Dattner obtained the CSF from the 4th ventricle by an occipital puncture to the cisterna magna. For the next month I monitored the progress of the patients by CSF measures obtained by ventricular taps. I assumed that it was a customary procedure, despite the risk of penetrating ("pithing") the brain stem. The procedure is now considered too riskful to be considered even by experienced neurologists.

Neurosyphilis is a late development in the life course of syphilitic disease, 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 of mercury and arsenic. 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 white cell counts and the concentration of protein in the CSF offered better and more reliable criteria of the severity and activity 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.

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.

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 the dexamethasone suppression tests in melancholia and the lorazepam response test in catatonia.

Personally Experiencing Psychoactive Drug Effects. 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.[72]

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 the 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 bone fragments and tissue debris, washed wounds with sterile saline solutions, created a plaster protective shell to immobilize the limb, and applied live maggots for days at a time. Maggots digested pus and wound debris, 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.

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 also relieved catatonic refusal of food, mutism, and posturing. I do not recall the use in stuporous catatonic patients, a use that became a central interest four decades later.

InterneshipTraining 1945-6

My first Random Controlled Trial; Penicillin in Empyema

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 I 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 patients randomly assigned by the odd or even final number of their chart record. Supplies of "x" were locked in a safe in the hospital director's office. Withdrawn samples were carefully recorded according to the patient's chart number. Within a few weeks the superiority of substance "x" became apparent, even to a neophyte physician – thick 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 Hispanic woman with empyema was admitted with her nursing infant. The random medication assignment was for sulfadiazine 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 ordered my suspension from the internship. I had broken two rules, direct orders of an Attending physician and the research protocol. Cooler heads prevailed a few days later and I was re-instated but the lesson of adherence to research assignment was learned. (Compound "x" was penicillin.)

Work schedules were exhausting, with 48 hours *on call* frequent, with 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 provide today. I joined him often and soon I was called to attend the autopsies of patients we had examined together. The logic of the symptoms and course of illness and the demonstrated neuropathology was impressive.

Residency Training: 1948-1952

New Science of Percutaneous Carotid Angiography

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. The technology of 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. 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 any abnormal images. I became skilled in obtaining cerebrospinal fluid and used the technique in later studies. The films showed tumors, bleedings, and encephalopathies, directing neurosurgical intervention when appropriate.[73]

Montefiore Hospital was a museum of chronic neurological disorders under study for decades. The film library included examples of classic syndromes of abnormal motor movements and seizures that I viewed to properly label peculiar repetitive 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 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. Studies of the CSF showed no persistent abnormalities as a result of these tests.

After one such procedure, a young man lay in bed, alert, relaxed, staring into space. Asked what he was seeing and pointing to objects in the room, he pleasantly confabulated responses of imaginary objects. He had developed an acute syndrome of visual neglect and denial of blindness known as the Anton Syndrome. 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. It was a lesson in applied psychodynamic philosophy to psychopathology.

Other clinical experiences were as intriguing. The popular folk singer Lead Belly -- Huddie Ledbetter -- was admitted with advanced amyotrophic lateral sclerosis. No effective treatment was known but my teachers 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 molecule 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.

Double Simultaneous Stimulation: The Face-Hand Test

Two teachers, Morris B. Bender and Edwin A. Weinstein encouraged my interest in clinical research during my neurology residency at Bellevue Hospital. 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 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 gross brain dysfunction, the *organic mental syndrome*.

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.

Intravenous injections of amobarbital increased omissions and displacements. Sensory errors increased during the course of electroshock therapy (when slow waves in the EEG became prominent after 3 to 9 seizures) when brain functions were altered.

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

Book Nine: Personal Biography

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 externship 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. She was much courted and married Julius on March 12, 1922, in her third year of training. I was born within a year. 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 Lowenthal, who had been sent by the family from New York.

A Greek scholar Lazaros Triarhou published a report on the faculty and students at the Wagner-Jauregg clinic in Vienna when W-J received the Nobel Prize in 1927. A class picture shows the faculty and cites 6 women graduates who went on to careers in neurology and psychiatry. He portrays two graduates, Alexandra Adler and Edith Klemperer, who were consultants during my residency days at Bellevue and my work at Hillside. Thinking of their education, I realized that they were students in Vienna in early 1920s, likely classmates of my mother Bronia, who left her education because of pregnancy. She tried to return to medicine in 1950, was not accepted, and graduated the Columbia University School of Social Work in 1953.

In the picture, Josef Gerstmann, Bernhard Dattner, and Paul Schilder appear, scholars who taught at Bellevue New York University during my schooling. Dattner was particularly instrumental in developing my interest in tests and diagnosis.

In our family setting, I always "knew" that I would become a physician. Admission to medical school in the U.S. was limited by the publicly acknowledged 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 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 tests of blood and urine, 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, 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 me, 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. Other students had measured the mitoses in the 24 to 48 hour and 72 to 96 hour cycles. (As I recall, the light cycle did not affect the rates of mitoses.)

During medical 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.

Students 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 the invasion as classmates canoed back from Lake George Village.

I came of age in America during the war years of the 1940s and 1950s, and for seven decades I have been a treating clinician and researcher, caring 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 to 170,000 in 2014 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 1960s brought new psychoactive medicines that changed brain chemistry and physiology, with resultant improvements in behavior, encouraging a massive deinstitutionalization, pushing tens 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. Identifying the benefits and developing treatment protocols for these new medicines became a professional challenge. As the effects of the new agents were measurable in the electrical

readings of the scalp recorded electroencephalogram (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 an effort to rescue the disorder of catatonia from its entombment within the poorly understood concept of schizophrenia and show it as an independent, identifiable, verifiable, and fully treatable syndrome. Bringing it out of its closet encouraged worldwide recognition and improved diagnosis and effective care. Catatonia is unique among the behavior disorders in having two effective treatments and a useful verification test, which makes each 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 decade organizing Hillside Hospital's research facilities, a brief stint to establish a Psychiatric Research Institute in Missouri, back to New York for a continuing academic career in different hospitals, then spending 35 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.

Family Affairs.

I married Martha Pearl Gross, a graduate of Barnard College on September 11, 1949. We had 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 for his care. After I called on her parents at their home in Great Neck, we dated and married 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. Our son, Jonathan was born on May 2, 1951, our daughter Rachel September 29, 1956, and our daughter Linda June 3, 1958.. In early 1953 we bought a home in Russell Gardens at 11 Wensley Drive.

Dalliance with Psychoanalysis: School and Personal Analysis

My interest in psychoanalysis developed during my classes in Texas in 1946. The enthusiasm for Freudian psychodynamic theory and practice rapidly infected American psychiatric teaching and practice. Beliefs that Freudian images explained the behaviors of the psychiatric ill and also offered effective treatment, personal understanding, and clinical relief flashed through clinical psychology, psychiatry, and popular culture in the theatre, film, and education. As a military

veteran, I was entitled to educational training supported by the GI Bill and like many peers, I decided to attend an analytic training program. The New York Psychoanalytic Institute and Columbia University programs required full-time attendance and clinic care of psychiatric patients but the William Alanson White Institute organized its classes during evenings and week-ends. 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 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 a 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.[74]

Another study also failed to support the psychodynamic suggestion that homosexuality was a root of paranoia. I was assigned the care of a 26-year-old Jewish married man with severe panic episodes. The faculty diagnosis varied between a neurosis with homosexual panic and 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. 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 patients effective treatment with imipramine.

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 medical research career.

Military career and travels as ship's surgeon

My active military service as medical officer 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. 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.

After completing basic military training I was assigned to Kentucky's 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.

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. As a member of an Officer's Board to decide on the qualifications for soldiers desiring to remain in the post-war career Army and as the panel psychiatrist I used interpretations of 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 merit-awarded soldiers were recommended for retention. At the end of November 1947 my service was suddenly ended after 20 months active duty.

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 the 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. 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, Peru, and Chile. 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 port health inspectors as they surveyed the ship in each port.

It was possible to visit port cities during one to two days of loading and unloading cargo. I visited the local mental hospital in Lima where Honorio Delgado, a leader in psychoanalysis, 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, patient drawings and paintings adorned the walls of the wards. These paintings were fore-runners of the 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. 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 traveled to Palermo (Sicily), Naples (Italy), and Valleta (Malta). The ship had a large medical complement and the work was easy.

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."

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 an academic affiliation as Research Professor at Washington University School of Medicine. We found a home in the Lake Forest suburb, and our children were soon registered in the community 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 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 community schools. Martha began teaching students at the elementary school in Port Washington and then in 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. I had exceptional students in Richard Abrams, Michael Taylor, and Robert Levine and was fortunate in the collaboration of Rhea Dornbush, Jan Volavka, Jiri Roubicek, 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. Interested in leasing a summer home in the Adirondacks in May 1972 Martha and our daughters flew to Lake Placid. My last flights as pilot 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 to New 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, EEG, and ECT studies at that facility.

Martha and I bought a home in Nissequogue 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. 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 in marine biology from Cornell and Duke Universities and then taught at Mt Holyoke College in Massachusetts. Linda received her undergraduate degree from Amherst College, among the first women after the college became co-ed, and her doctorate in entomology at University of Florida in Gainesville. She began a teaching career at Sweet Briar College in Virginia. Each married at our Nissequogue home and soon the family grew with four grandchildren.

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. (The CORE studies.) For various administrative reasons I was unable to carry out my portion of the 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 to pursue writing. Since 1999 I have wrtitten 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 2019.

Martha died suddenly on March 31, 2016. I remained at my Long Island home spending my time writing. By 2018, I established a second home in South Hadley, Massachusetts with my daughter Rachel. In June 2019 I sold my Long Island home and moved to Rachel's home in South Hadley, Massachusetts.

Books Authored by Max Fink

Electroencephalography in Human Psychopharmacology. EEG Journal, Supplement 23, 1964. NY: Elsevier.

Convulsive Therapy: Theory and Practice. NY Raven Press, 1979.

ELECTROSHOCK: Restoring the Mind. Oxford U Press, New York, 157 pp., 1999.

Electroshock: Healing Mental Illness. NY: Oxford U Press. 2002.

Ehics in Electroconvulsive Therapy. NY: Routledge. 2004. (Ottosson J-O, Fink M.)

Catatonia: A Clinician's Guide to Diagnosis and Treatment. Cambridge UK: Cambridge U Press, 2003 (Fink M, Taylor MA.)

Rediscovering Catatonia: The Biography of a Treatable Syndrome. Acta psychiatr Scand. 127: Supplement 441;1-50, 2013.

The Madness of Fear: A History of Catatonia. NY: Oxford University Press, 2018. (Shorter E, Fink M.)

Melancholia:The Diagnosis, Pathophysiology, and Treatment of Depressive Illness. Cambridge UK: Cambridge University Press, 2006. (Taylor MA, Fink M,)

Endocrine Psychiatry: Solving the Riddle of Melancholia. NY: Oxford U Press. (Shorter E, Fink M.), 2010.

Edited Books:

Fink M. (Ed.) *Convulsive Therapy. Seminars in Psychiatry*. Grune & Stratton, 1972.

Fink M, Kety S, McGaugh J, Williams T. (Eds): *Psychobiology of Convulsive Therapy.* Washington, DC, V.H. Winston and Sons 1974.

Bradley P, Fink M. (Eds): *Anticholinergic Drugs and Brain Functions in Animals and Man,* P. Bradley and M. Fink (eds.), *Progress in Brain Research,* Vol. 28, Elsevier, 1968.

Dornbush RL, Freedman AM, Fink M., *Chronic Cannabis Use.. Annals N.Y. Academy of Sciences, 282:* 430 pp., 1976.

Stefanis C, Dornbush RL, Fink M. *Hashish: A Study of Long-Term Use* (eds.). New York, Raven Press, 181 pp, 1977.

[1] ***Archives:*** When the historians Edward Shorter and David Healy visited my home in 2006 to examine my files and books for their history of the shock therapies, they were impressed by the extent of the files and asked what I planned to do with them.[1] They encouraged their being publicly archived. The Stony Brook University Library archivist Kristen Nyitray examined and agreed to archive the collection. These files are established as the Max Fink Archives in the Special Collections at the Main Library of Stony Brook University. I also deposited my library; these books are indexed in the University files and in WorldCat.

Contact: Kristen J. Nyitray, Head, Special Collections and University Archives, University Archivist, Associate Librarian, Stony Brook University.

< kristen.nyitray@stonybrook.edu>
t: 631.632.7119 / f: 631.632.1829

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

[3] Fink M Shaw R, Gross G, Coleman FS. Comparative study of chlorpromazine and insulin coma in the therapy of psychosis. *J. Amer. Med. Ass.*, 1958; 166: 1846-1850

[4] Sylvia Nasar's biography A Beautiful Mind was filmed; I was the consultant to the producers in the making of the film. Discussed in Book Three.

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

[6] Fink M, Bolwig T. Electrotherapy of melancholia: The pioneering contributions of Benjamin Franklin and Giovanni Aldini. *J ECT* 2009; 25:15-18.

[7] Beginning January 1953 with Hans Strauss and Mortimer Ostow I learned how to apply scalp electrodes, maintain the EEG recorders, and interpret the records. The Medical Director Joseph S. A. Miller, purchased a Grass electroencephalograph with a $5,000 grant from the Dazian Foundation obtained by Dr. Israel Strauss, the Founder of the Hospital.

[8] In the 10 years of its existence, Ira Belmont, Martin A. Green, John C. Kramer, Max Pollack, Eric Karp, Donald F. Klein, Abraham Kaplan, Arthur Willner, Karl Andermann, Joseph Jaffe, Hyman Korin, George Krauthamer, Nathaniel Siegel, Henry J. Lefkowits, Harold Esecover, and Barre Alan, collaborated in the studies. Arnold G. Blumberg of the Medical Department was an active collaborator..

[9] By 1977 in USA, Paul Blachly created an ECT stimulating device using brief pulse stimuli that recorded the EEG of the seizure. His device, labeled MECTA, has been widely adopted. The technology became world standard.

[10] Fink M, Kahn RL, Green M. Experimental studies of the electroshock process. *Dis. Nerv. Syst.*, 19: 113-118, 1958.

[11] In the last two decades, ECT has been denigrated as a "neurostimulation." Since neurostimulation devices are applied in neurotic depressed and character disordered subjects, increased outpatient usage has changed the character of modern treatment to encompass low energy, short seizure, RUL placement treatments that fail to influence severely ill, but act mainly as placebo psychotherapiess similar to the weakened SSRI, SNRI antidepressants and atypical neuroleptics that dominate outpatient care since the 1990s.

[12] 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. *Acta Psychiatr Scand* 2010; 122: 173-183.

[13] The question is the basis for the neuroendocrine hypothesis of ECT, that the seizure pattern is based on systematic changes sensed by pathology in the organism that can be redressed, much as a sneeze or a cough clears physical passages.

[14] Bennett, A.E. The introduction of curare into clinical medicine.Present and potential usefulness. *Am Sci* 46; 34:434-431.

[15] While on a lecture tour in 5 cities in India in 1991, the first question at each site was my attitude to the use of unmodified ECT, inducing seizures without sedation and motor relaxation. When I expressed my experience, recalling the benefits of my first experiences at Hillside in 1952, I opined "unmodified ECT is better than no ECT." The audience applauded. The argument persisted for many years as the cost of the agents and the fee of the anesthesiologist surpassed the reimbursements for the ECT procedure.

[16] When the anti-psychiatry cries of psychologists became strident again in 2020s, with claims that ECT had not been properly tested in an RCT with sham ECT. The sham-ECT study data was republished in 2001 in *JECT*.

[17] Palmer RL. *Electroconvulsive Therapy: An Appraisal*. NY: Oxford U Press, 1981

[18] Fink M, Kahn RL, Karp E, Pollack MA, Green MA, Alan B, Lefkowitz HJ. Inhalant-induced convulsions. *Arch. Gen. Psychiat.,* 4: 259-266,1961.

[19] 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.

[20] Fink M, Greenberg LB, Gage J, Vikun S. Isoflurane anesthesia therapy: A replacement for ECT in depressive disorders? *Convulsive Ther* 1987; 3: 269-277.

[21] Fink M. Cholinergic aspects of convulsive therapy. *J. Nerv. Ment. Dis., 1966;* 142: 475-484.

[22] The results are widely published by Robert Kahn, Max Pollack, and Ira Belmont. The results are summarized in *Convulsive Therapy: Theory and Practice*, NY: Raven Press, 1979.

[23] We received four-year funding from NIMH for the project. 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.

[24] This is my second study reporting the greater efficacy of seizures induced by bilateral electrode placements. The CORE study replicated again.

[25] Fink M, Abrams R, Volavka J, Roubicek J, Dornbush R. Lateralized EEG changes after unilateral and bilateral electroconvulsive therapy. *Dis. Nerv. Syst.,* 31 (11) Suppl.: 28-33, 1970.

[26] Wachtel LE, Dhossche DM. Self-injury in autism as an alternative sign of catatonia: implications for convulsive therapy. *Med Hypotheses* 2010; 75(1):111-4.

[27] Bright-Long L, Fink M. Reversible dementia and affective disorder: The Rip van Winkle Syndrome. *Convulsive Ther* 1993; 9: 209-16.

[28] Greenberg LB, Mofson R, Fink M. Prospective electroconvulsive therapy in delusional depressed patient with a frontal meningioma. *Br J Psychiatry* 1988; 153: 105-107.

[29] Petrides G, Fink M. Atrial fibrillation, anticoagulation, and electroconvulsive therapy. *Convulsive Ther.* 1996; 12: 91-98

[30] 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., 183-193, 1978.

Fink M. EST and other somatic therapies of schizophrenia. In L. Bellak (ed.): *Disorders of the Schizophrenic Syndrome*. Basic Books, New York, 353-363, 1979.

Fink M., Sackeim HA. Convulsive therapy for schizophrenia? *Schizophrenia Bull.* 1996; 221: 27-39

[31] Fink M, Taylor M.A. The medical evidence-based model to identify psychiatric syndromes: Return to a classical paradigm. *Acta Psychiatr Scand* 2008; 87: 81-84 .

[32] I did not believe that ECT augmentation of clozapine in clozapine non-responders was effective. When George Petrides, with the encouragement of John Kane to publish a "positive" report, I withdrew my association. Augmentation by ECT of fluphenazine and chlorpromazine treatment in psychosis are better documented.

[33] Greenberg LB, Zervas I, Suckow RF, Cooper T, Jandorf L, Fink M. Rat brain concentration of fluphenazine during a course of electroconvulsive shock. *Convulsive Ther* 1990; 6: 273-9.

[34] I moved the study site to Hillside Hospital with George Petrides as Principal Investigator.

[35] Fink M. What was learned: Studies by the Consortium for Research in ECT (CORE) 1997-2011. *Acta Psychiatrica Scand*. 129: 417-426, 2014.

[36] Fink M, Taylor MA. Electroconvulsive therapy: Evidence and challenges. *JAMA* 2007; 298: 330-332 .

[37]Abrams R. *Electroconvulsive Therapy*. Edition IV. NY: Oxford University Press, 2002.

[38] Meduna L: *Die Konvulsionstherapie der Schizophrenie*. Halle Germany, Karl Marhold, 1937.

[39] Fink M. (Ed.): *Convulsive Therapy* (ed.). *Seminars in Psychiatry* 4: 1. Grune & Stratton, Inc., New York, 70 pp.

[40] Fink M, Abrams R, Bailine S, Jaffe R. Ambulatory electroconvulsive therapy. Ta force report of the association for convulsive therapy. *Convulsive Ther.* 1996; 12: 42-55.

[41] Fink M. Complaints of loss of personal memory after electroconvulsive therapy: Evidence of a somatoform disorder. *Psychosomatics* 2007; 48:290=293.

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

[43] Fink M. A unified theory of the action of physiodynamic therapies. *J. Hillside Hosp.*,1957; 6: 197-206.

[44] Fink M, Ottosson J-O. A theory of convulsive therapy in endogenous depression: Significance of hypothalamic functions. *Psychiatry Research* 2: 49-61, 1980.

[45] Fink M. The mode of action of convulsive therapy: the neurophysiologic-adaptive view. *J. Neuropsychiat.,* 3: 231-233.1962.

[46] Fink M. Cholinergic aspects of convulsive therapy. *J. Nerv. Ment. Dis., 1966;* 142: 475-484.

[47] Nemeroff C, 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.

[48] Fink M, Kety S, McGaugh J, Williams T. (Eds): *Psychobiology of Convulsive Therapy.* Washington, DC, V.H. Winston and Sons

[49] Kahlbaum KL. *Die Katatonie oder das Spannungsirresein: eine klinische Form psychischer Krankheit*. Berlin: Verlag August Hirshwald, 1874.

[50] Greenberg LB, Gujavarty K. The neuroleptic malignant syndrome: Review and report of three cases. *Comprehens Psychiatry* 1985; 26:63–70.

[51] Taylor MA. Catatonia: A review of a behavioral neurologic syndrome. *Neuropsychiatry, Neuropsychology Behavioral Neurology*. 1990; 3(1):48-72.

[52] Rogers D. *Motor disorder in psychiatry*. Chichester UK: John Wiley & Sons, 1992.

[53] Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia: I: rating scale and standardized examination. *Acta psychiatr. Scand* 1996; 93 (2): 129-36.

Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia: II. Treatment with lorazepam and electroconvulsive therapy . *Acta Psychiatr. Scand* 1996; 93 (2):137-43.

[54] Shorter E. *What Psychiatry Left Out of DSM-5.* NY: Taylor & Francis, 2015.

[55] Taylor MA. *Hippocrates Cried: The Decline of American Psychiatry*. NY: Oxford U Press, 2013.

[56] Taylor M, Fink M. Fink Catatonia in psychiatric classification: A home of its own. *Am J Psychiatry* 2003; 160: 1233-1241.

[57] Fink M, Shorter E. Does persisting fear sustain catatonia? *Acta Psychiatr Scand* 2017; Nov; 136(5):441-444.

[58] Our experience together had been at New York Medical College during his residency training and when he and his colleague Richard Abrams joined the Stony Brook University faculty.

[59] Clinicians versed in ECT see the rapid response of catatonia and melancholia, in their varied forms, to repeated induced seizures. The DSM commissioners, all five teams from 1952 to 2013, lacked members with experience in ECT. Many were known opinion leaders and paid consultants to industry, with ambulatory office practices and little experience with the severely ill, so had no experience with the many forms of catatonia and melancholia. Further, in the decades from 1980 to 2013, they were paid well as industry consultants to support the new agents, the SSRI, SNRI, and atypical neuroleptics, and reject the tricyclic antidepressants (imipramine, amitriptyline) and the typical neuroleptics (chlorpromazine, fluphenazine) as toxic.

[60] Fink M, Klein DF, Kramer J. Clinical efficacy of Chlorpromazine-Procyclidine combination, Imipramine and placebo in depressive disorders. *Psychopharmacolgia (Berl.),* 7: 27- 36.

[61] Davies BJ, Carroll BJ, Mowbray RM: *Depressive Illness: Some Research Studies*. Springfield, IL: C. C Thomas, 1972.

[62] Papakostas Y, Fink M, Lee J, Irwin P, Johnson L. Neuroendocrine measures in psychiatric patients: Course and Outcome with ECT. *Psychiatry Res* 1981;4: 55-64.

[63] Glassman A. APA Task Force on Laboratory Tests in Psychiatry: The Dexamethasone Suppression Test in Psychiatry. *Am J Psychiatry* 1987;144:1253-1262

[64] Fink M, Rush J, Knapp R, *et al.* DSM melancholic features are unreliable predictors of ECT response: A CORE Publication. *JECT* 2007; 23(3): 139-146.

[65] Taylor MA, Fink M. *Melancholia: The Diagnosis, Pathophysiology, and Treatment of Depressive Illness.* NY: Cambridge University Press, 2006.

[66] Bolwig T, Shorter E. *Melancholia: Beyond DSM, Beyond Neurotransmitters*. *Acta Psychiatrica Scandinavica* Supplement 433; 115:1-183, 2007. Participants included, in addition to the Editors, Gordon Parker, Michael Taylor, William Coryell, Athanasios Koukopoulos, Donald Klein, Bernard Carroll, Jules Angst, Walter Brown, Max Fink.

[67] Taylor M. *Hippocrates Cried. The Decline of American Psychiatry*. NY: Oxford University Press, 2013.

[68] Shorter E, Fink M. *Endocrine Psychiatry: Solving the Riddle of Melancholia*. NY: Oxford University Press, 2010.

[69] Bradley P, Fink M. (Eds): *Anticholinergic Drugs and Brain Functions in Animals and Man. Progress in Brain Research,* Vol. 28, Elsevier, 1968.

[70] Fink M. EEG classification of psychoactive compounds in man: review and theory of behavioral associations. *Psychopharmacology: A Review of Progress,* 1957-1967: D. Efron, J. Cole, J. Levine and J.B. Wittenborn (eds.): U.S. Govt. Printing Office, Washington, DC, pp. 497-507.

[71] Fink M. Remembering: the forgotten neuroscience of pharmaco-EEG. *Acta Psychiatr Scand* 2010; 121: 161-73.

[72] In my schooling, self-administration of trial medication was accepted as part of my educational experience. By 1980s, a change had occurred among students. When teaching psychopharmacology I offered self-exposures to various psychoactive medications,many of which I had experienced. The students refused, and I was admonished by the Dean that such teaching was not acceptable.

[73] As the death of President Kennedy was announced over the hospital radio, I was in the r-ray suite, inserting a needle in a patient's spinal canal for a PEG.

[74] Dr. Tarachow presented these findings at a meeting of the American Psychoanalytic Association in New York in 1953. I was denied admission to the meeting as I had not graduated from an accredited psychoanalytic institute.