Neglected Disciplines in Human Psychopharmacology
PHARMACO-EEG AND ELECTROSHOCK
Max Fink

You've been associated with, for my money, two of the really big stories in biological psychiatry/psychopharmacology: the rise and fall of the EEG and electrophysiology within psychopharmacology and the ECT story.

The story of EEG in psychopharmacology is one of a promise that is, as yet, unfulfilled. Perhaps, never to be fulfilled. When Hans Berger of Jena first reported that he had recorded the human EEG from the scalp of a human in 1929, he also described different effects of sedative, stimulant, and deliriant drugs. When the psychopharmacology revolution began in the 1950s, many psychiatrists were already trained in EEG and it was easy to look to the EEG to measure the effects of the different medicines. The new drugs came to us rapidly, but their identification and classification were confusing. We did not know what to expect, which symptoms should be the basis for our prescription. Many classifications were proposed, along the lines of chemical structure, effects on cardiovascular physiology, and the effects on motor activity in animals. The measures did not separate the new substances into clinically meaningful classes. None could be used with new drugs to identify their clinical usefulness. But the EEG measures identified the effects of different classes of medicines. That is, the measures could do so when tested in man. The EEG effects of the new drugs in animals varied inconsistently, mainly because the physiology and pharmacology of animal species varied. A controversy ensued when pharmacologists insisted that the effects of psychoactive drugs in mice, rats, cats, and dogs could predict the effects in man. That controversy severely weakened the industrial and academic interest in human pharmaco-EEG, so the discipline is still alive today in some parts of Europe and Japan, but sadly, it has no academic base in the United States.

The ECT story is more complex. Electroshock is the most remarkable treatment of severe mental illnesses. Except for penicillin in neurosyphilis, no treatment of mental illness is as effective for psychosis, for depressed mood, for manic attacks, and for the persistent relief of catatonia as is ECT. It even relieves parkinsonian rigidity. Despite its acknowledged efficacy and remarkable safety, the treatment is ignored and used as the last resort, after many medicines have failed. I became interested in ECT in 1952, and except for four years in the early 1960s when I was in St. Louis, it has been a very important clinical and research interest. I ended up having to choose between it and pharmaco-EEG.

How did you actually come into psychiatry?

I graduated medical school, the youngest member of my class, just as the war in Europe ended in 1945. During internship at a city hospital in New York, I became interested in neurology, and so stated in my induction papers into active military service in 1946. By that happenstance, the Army sent me to the School of Military Neuropsychiatry at San Antonio's Fort Sam Houston for an intensive four-month training course. It was a remarkable course, covering neurology,

clinical psychiatry, psychoanalysis, insulin coma, electroshock, and emergency psychiatry.

I was assigned to the Fort Knox Station Hospital as chief of psychiatry, responsible for three inpatient wards, each of about 20 patients, and an outpatient clinic. A unit, reserved for psychotic patients, was dedicated to insulin coma and electroshock. Considering my later interest, I have no recollection of those cases. They were managed by the nurses and other doctors.

My 20 months military service was stateside, and with thousands of others I was demobilized in November 1947, four months before my tour of duty was scheduled to end. I held a residency appointment in neuropsychiatry for July 1948. Faced with six months free time, I could, of course, have taken up my training earlier. Instead, I joined the Grace Line as a ship's surgeon, taking three trips to the west and north coasts of South America. A berth with the American Export Line in April 1948 brought me to the Mediterranean and my first, of many, visits to Naples and Rome. On the return from one of the Grace Line trips I met Martha, who met her parents at dockside, and we married in 1949.

At the neuropsychiatry program at Montefiore Hospital in New York, I learned clinical neurology and became experienced in pneumoencephalography and percutaneous cerebral angiography. My next stint at Bellevue Hospital introduced me to electroshock, lobotomy, fourth ventricle and spinal taps for CSF, neurosyphilis and fever therapy, and to psychoanalysis. My mentors at Bellevue, Morris Bender, Edwin Weinstein, and Hans Lukas-Teuber started me on a research career in sensory physiology and psycholinguistics. Bender assigned me to collect data from a very diverse population for the Face-Hand Test, a test of double simultaneous tactile stimulation. His meticulous instructions in sampling, data collection, and reporting became guideposts for my career. Our publications between 1950 and 1956 laid the groundwork for the science of 'soft sign' brain dysfunction.

Teuber argued for quantitative measures in sensory testing, and in 1957, Hyman Korin and I reported the role of the strength of stimulus in the phenomena of displacement and extinction in these tactile tests.

What sparked your interest in research?
Well one of the things was the study of language changes when subjects were under the influence of amobarbital. Ed Weinstein and Robert Kahn had shown that patients whose brain functions had been compromised by tumor or by head trauma denied their illness or minimized their symptoms when given set doses of amobarbital. The language changes were examples of the interaction of psychodynamic defense mechanisms and changes in brain function. Their descriptions became the basis for a theory of the mode of action of ECT.

My military schooling had encouraged me to believe that psychoanalysis was an important element of clinical practice and despite an anti-psychodynamic posture by my Bellevue teachers, I enrolled in the William Alanson White Institute for psychoanalytic training in 1948 and was certified after completing a personal analysis in 1953. Psychoanalysis was in such bad repute among neurologists that I kept my interest and training secret. I seem to have learned little that was useful, however, and after a few years of psychotherapy practice in which I applied what I had been taught, I put these teachings aside.

In January 1952, I went to Hillside Hospital for my fifth year of training. The hospital was known for its psychodynamic focus in both the treatment of patients and the training of its residents. Fully one-third the patients received somatic treatments and the training in these treatments was intensive. My first assignment, on January 2, was to the electroshock and insulin coma unit.

I was certified in neurology, by the American Board of Neurology and Psychiatry, in 1952 but I wanted additional research experience and applied for a National Foundation for Infantile Paralysis fellowship in 1953. I studied electroencephalography with Hans Strauss, the author of a standard textbook at the time, and applied the Weinstein amobarbital and Bender Face-Hand tests to patients undergoing electroshock and insulin coma.

I opened an office for the practice of neurology and psychiatry in Great Neck, Long Island in the fall of 1953 and took my Board examinations in psychiatry the next year. After the fellowship year, I became the attending psychiatrist in charge of the insulin coma and electroshock treatment programs at Hillside. This position gave me the opportunity to continue my research interests, but I needed an electroencephalograph which, at the time, was not available at the hospital. The Medical Director, Joseph Miller turned to the President of the Hillside Board, Dr. Israel Strauss, for help and within a few weeks I had received a $5,000 grant from the Dazian Foundation. It seemed very easy to launch a research career.

What was your first independent research project?
As I developed an EEG service, I studied the patients undergoing electroshock. ECT was such a fine subject of study -- patients were repeatedly treated, at set times, and the changes in brain function developed gradually and cumulatively, allowing us to chart the changes that occurred week by week. EEG is non-invasive and our subjects welcomed the attention that they received in the laboratory. The recovery process could also be studied as the patients slowly reintegrated in the weeks after the treatment course ended.

A progressive slowing of EEG frequencies is normally observed during a course of electroshock. Normally, the EEG exhibits rhythmic oscillations between 9 and 11 cycles per second, but after a series of seizures, the mean frequency slows to 4 to 6 Hz, and the amplitudes increase. An intravenous injection of amobarbital exaggerates the slowing of frequencies. Patients who develop EEG slowing after

amobarbital in their first few ECT have good clinical outcomes; those who fail to produce such slowing, do poorly, despite further treatments. Martin Roth first described this finding in 1951.

We also looked at the interseizure EEG, without provocation by amobarbital, and found that patients who developed persistent high degrees of EEG slowing early in the treatment course have good clinical outcomes. Those who, despite extensive treatment, fail to develop EEG slowing, fail to show a good clinical response. This new finding, published in 1956, was neglected for decades, the years during which ECT research came to a standstill. It has had a renewed life in present-day ECT practice as a useful marker of good outcome by the elegant work of Harold Sackheim at Columbia University.

These experiences with EEG led to my first NIMH award (MH-927) in 1954, for the study of the EEG effects of electroshock. The award led the hospital to establish a research department, one that I named the Department of Experimental Psychiatry. It grew rapidly and the interests of the research team quickly broadened. The foundation of a research department allowed us to study the effects of the psychotropic drugs that were fortuitously introduced at that time.

How did you get involved in the new psychopharmacology?
LSD came to my attention in 1953 and we thought to measure its effects on speech and on the EEG. We, the researchers, were the first subjects, then our residents-in-training, and then our patients. Self-administration of medicines was an accepted part of pharmacology training in medical school and a justification for human research. The tiny amounts of intravenous LSD, one thousandth of a milligram, elicited well-publicized illusory and mood altering effects. The EEG effects were strikingly different from those we had observed with ECT and with amobarbital. In fact, LSD reversed the EEG slowing produced by ECT! We had a glimmer of EEG specificity for different agents.

Soon thereafter, I was invited to a meeting at the Creedmoor State Hospital, organized by Henry Brill of the New York State's Office of Mental Health, to discuss the statewide experience with the new drug Thorazine. In presentation after presentation during a long and exciting day, doctors from the state services described the remarkable effects of chlorpromazine in relieving excitement, aggressivity, and psychosis. While each study's sample size was small, the descriptions were so congruent, that each of us in the audience avidly sought samples from the representative of Smith, Kline & French.

I gave Thorazine to excited, psychotic patients, who miraculously calmed quickly. Within a few weeks the word was out and I received calls from nurses from different units in the 200-bed hospital to offer me the names of patients who might be suitable for Thorazine. Yes, it effectively reduced aggression, hostility,

and psychosis, but we did not know the proper dosages nor did we know the risks.

Interestingly, of the first seven patients treated with Thorazine, three developed jaundice, a cause of concern. Yet the benefits were so dramatic, that we persisted in our experiments despite this hazard. Dosages were often increased rapidly, and patients exhibited muscular rigidity, dykinesia, and parkinsonian signs. While these findings were disturbing, the benefits were so much more striking, that we were enthusiastic about continuing Thorazine's use. Some European authors saw the motor signs as essential to treatment efficacy, so much so that their development was welcomed.

For the next few years, we carried out both clinical and EEG studies of new drugs and ECT. An opportunity to make a direct comparison between chlorpromazine and an established treatment presented itself in a study of insulin coma. In 1956, I was in charge of the insulin coma treatment unit. It was a terrible treatment. It was difficult to administer safely, the results were poor, and every year at least one patient died. We had seen some benefit from chlorpromazine, so I proposed a study to the Medical Board; that we assign the patients referred for insulin coma to either insulin or chlorpromazine. The study was done and a year later, after we had treated 54 patients, we reported that both chlorpromazine and insulin coma affected psychotic patients similarly. Chlorpromazine was as effective as insulin coma, easier and less expensive to use, and much safer. Our report in JAMA was a methodologic milestone for that early era in psychopharmacology, involving random assignment of patients, assessments by independent raters, and the use of quantitative, itemized rating scales. It was one of two reports examining insulin coma at the time. The other, by Brian Ackner, found barbiturate coma to be as effective as insulin as well as safer. A few years later, I found a third report, in the Czech literature, comparing insulin coma and another neuroleptic, with the same conclusion.

Within a year, our insulin coma unit was closed. The insulin coma study was one of the more important ones that I have done, not only because it was instrumental in ending the use of insulin coma, but also in showing the Medical Board of Hillside Hospital that they could get clinical, academic, and financial advantages from our research. Before that study, they were supporting research with their heads. Thereafter, support came from their hearts and pocketbooks. In 1960, they built a research building on the Hillside campus, a site that is still the center of Hillside Hospital's research.

We next studied the EEG effects of chlorpromazine. Again, the EEG patterns were easily distinguishable from other medicines. In 1957, we examined Geigy’s Tofranil, said to be antidepressant in action. During our clinical trials, we found an EEG signature that differed from those of chlorpromazine, LSD, and ECT. We thought that we had a valid system of drug classification, and presented this experience at the 1958 meeting of the CINP in Rome.

It was a productive meeting. Dieter Bente and Turan Itil of Nuremberg, Germany, had submitted an abstract on the same topic and we were scheduled to speak in the same session. We had not known of each others' work, but that afternoon we realized that we could exchange our slides and give our talks from the others' slides! A friendship flourished, and a few years later Turan Itil joined me at the Missouri Institute of Psychiatry, where we developed digital computer methods to analyze EEG. Turan developed the systematic classification of psychoactive drugs, a four-axis system, which was most successful. The foundation of the science of pharmaco-EEG was laid at that meeting when we realized that psychoactive compounds with different clinical applications had different EEG signatures.

What were the next developments in your clinical studies?
We examined the effects of central anticholinergic drugs, such as diethazine, JB-318, JB-336, and the antiparkinson agent, procyclidine. These agents gave us yet another EEG profile in our patients. The profile of imipramine resembled that of these anticholinergic drugs. We inferred that imipramine had central anticholinergic activity, and I presented these findings and conclusion at a McGill University meeting in Montreal in March 1959. The idea that Tofranil had anticholinergic activity was new, and it was ridiculed by the Geigy pharmacologists at the meeting, as contrary to their laboratory assessments. Further study showed that we were right, and indeed, it is the anticholinergic activity of the tricyclic antidepressant drugs that is now thrown at them as their defect by the marketers of the SSRI drugs. The anticholinergic classification of imipramine in EEG was another difference in findings of studies in man and in animals.

We examined every new substance that we could reasonably give to our patients. Anticholinergic drugs blocked the EEG slowing associated with electroshock. Depressed patients who improve with ECT are less depressed and they deny their symptoms. Their EEG is filled with slow waves. When given atropine or scopolamine, the behavior changes and they complain of being depressed, of their anger, irritability, and suicidal thoughts. This effect wore off after a few hours with the metabolism of the medicines. The EEG slowing returned when their mood improved. We concluded that the EEG slowing - and clinical improvement - in electroshock were due to an increase in the brain's cholinergic activity. Could this be the basis for the antidepressant effect of ECT? Using associated findings from human and animal trauma studies, and from CSF studies in patients with epilepsy, I concluded that the neurohumoral mechanism for ECT did lie in an increase in acetylcholine activity, and published this hypothesis in 1966.

The research team at Hillside's Department of Experimental Psychiatry expanded rapidly as our clinical and our EEG studies were in the mainstream of clinical psychopharmacology. The psychologists Robert Kahn, Max Pollack, Ira Belmont,

and Nathaniel Siegel described the effects of the new medicines and ECT on speech patterns and on neuropsychological tests including the Rorschach and figure-ground tests. Donald Klein, John Kramer, and Joseph Jaffe, clinician researchers, described the clinical effects of the new medicines. Martin Green was the neurologist who managed both our ECT and EEG studies.

Clinical studies became our major focus, with the EEG and neuropsychological findings soon becoming secondary. As rating scales, quantification of signs and symptoms, and statistical methods became established for clinical psychopharmacology, these were increasingly employed. Our comparisons of insulin coma with chlorpromazine and of ECT with the inhalant flurothyl were two authoritative studies that influenced clinical practice. But it was the chlorpromazine, imipramine, and placebo study that had the most effect on our knowledge.

It is hard to realize now that when the new medicines were introduced, we did not know what their effects might be. Our classification of mental disorders relied on DSM-II, a classification based on psychodynamic principles, with most syndromes described as 'reactions' to unconscious conflicts. The new medicines were first seen as antipsychotic, they were even labeled antischizophrenic, but what were their effects on mood disorders and on the psychoneuroses? We had difficulty in identifying syndromes, and in describing drug effects. Hamilton, Lorr, Clyde, and others had introduced item based rating scales to assess change but how to relate the drug effects to diagnoses remained a mystery. The same problem faced us in assessing the EEG profiles of the medicines, how best to describe their effects on clinical syndromes?

Because researchers controlled the use of the new drugs at Hillside Hospital, we were able to organize a remarkable study. All patients, regardless of clinical diagnosis, referred for any of the new drugs were randomly assigned to one of three treatments, chlorpromazine, imipramine or placebo. Patients receiving chlorpromazine also received procyclidine to minimize parkinsonian effects. All medications were presented in liquid vehicle, with dosages increased weekly to maxima of 1200mg chlorpromazine, 300mg imipramine, or an equivalent of placebo vehicle. Patients were rated weekly using a variety of item-rating scales. We confirmed the antipsychotic effects of chlorpromazine, the antidepressant effects of imipramine, and the limited efficacy of placebo in our psychotic and manic patients. We also discovered that chlorpromazine was an effective antidepressant, a finding that heralded the observations two decades later of the efficacy of antipsychotic drugs in cases of delusional depression. An astonishing effect was the reduction in phobic symptoms in a group of adolescents treated with imipramine, a finding that encouraged Don Klein to pursue this application so thoroughly that it has become the basis for the present treatment of this disorder. Not all patients improved, and some, who were seen as suffering from adolescent schizophrenia, became disorganized, aggressive, and grossly psychotic when treated with imipramine. These observations were published in

the early 1960s and were considered so useful that Klein replicated the study in another sample over the next decade.

What was the next development in pharmaco-EEG?
We were very comfortable with our clinical and EEG studies. We were able to classify psychoactive drugs and define their clinical application. But could we predict the role of new entities accurately, before they were tested in the clinical marketplace? To do so, we examined the EEG effects of new compounds during their phase-1 and phase-2 pharmacology studies.

Turan Itil did a pharmaco-EEG study of mianserin (GB-94), an Organon compound, in normal male volunteers. Mianserin elicited an EEG profile that was similar to that of amitriptyline. When he reported his findings, the Organon pharmacologists doubted his report since mianserin had not met any of the preclinical tests for an antidepressant compound. I was asked to replicate his EEG finding, which I did easily. The research director, Jack Vossenaar organized clinical trials which quickly confirmed the prediction. Within two years, mianserin was in widespread clinical use throughout the world.

It became the best selling antidepressant in the UK and many parts of Europe.
The mianserin experience confirmed our view that animal trials of psychoactive compounds were not predictive of the substances' effects in man. As a result of the failure of the tests then in use to predict mianserin's clinical activity, Organon pharmacologists, led by Henk van Riezen and Roger Pinder, sought preclinical tests that were unique to mianserin. They developed and then used, I believe it is still used today, a mouse swimming test as a screen for a substance's antidepressant activity. This success of pharmaco-EEG led to the study of many compounds in the pharmaceutical pipeline. Within a few years, companies were contracting with laboratories in Berlin - Werner Herrmann, in Vienna - Bernd Saletu, in Genoa -Walter Sannita, in Paris -Pierre Etevenon, in Osaka - Masami Saito and in the United States with Turan Itil, Charles Shagass, Leonide Goldstein or me. Not only were the predictions of clinical application fruitful, but the failure to develop a definable EEG signature marked compounds as clinically ineffective.

An example is seen in our study of flutroline, a compound with a very prolonged duration of action in preclinical studies in dogs. It was looked upon as a possible "Saturday-night" antipsychotic, effective with a once-weekly administration. When we sought to define its clinical efficacy in psychotic patients, and examined its EEG pharmacodynamic profile, it was quite ineffective. Indeed, we had to give very large doses to elicit any behavioral effect. When we sought to exceed the preclinical safety data, we were enjoined from further study. The medication did not make it to the marketplace.

Organon had an active study program for peptides derived from ACTH and from beta-endorphin. Two compounds, GK-78 and OI-63 were thought to have CNS activity in preclinical trials, but neither affected behavior or EEG in our clinical trials, and while each is still undergoing laboratory testing, neither has achieved a role in clinical care.

6-azamianserin, now marketed as Remeron (mirtazepine) is another Organon compound which has both laevo- and dextro-enatiomers. In preclinical testing, one form was deemed to be active and the other inactive. We undertook pharmaco-EEG trials of both enantiomers and the racemic mixture, and found both enantiomers active in the EEG. Clinical trials were undertaken with the separate enantiomers and both were found to be clinically active.

Another application of pharmaco-EEG was to define a medicine's pharmacodynamic profile, to assess the period of peak action and its duration, findings that were useful in formulating dosage forms and schedules to assure effective clinical activity. A good example of this effort was in Itil's examination of the onset and duration of activity of different formulations of diazepam, some made by the patent holder and some by generic manufacturers. Itil was able to define differences in onset and duration that led to limitations in the sale of generic forms of diazepam.

Why the difference between the preclinical and the clinical studies?
Let's define the differences first, and try to explain them later. The preclinical studies used a variety of animals, each with its own pharmacology. To observe an effect, dosages were maximized. Observations of animal behavior are severely limited, mainly to motor responses, sleep and wakefulness, and in specially-trained animals to changes in test responses.

Animals differ in their pharmacology, both between species, and even within a species, with different genetic strains. Take the difference in response of cats and dogs to opioid substances. In one, opioids are excitatory, and in the other, sedating. Man's response is similar to that of the dog for such substances. Even within a species, animals exhibit marked differences in seizure threshold, drug toxicity etc. Such differences make it impossible to know in advance which animal species or genetic strain, of the myriads that are available, will show a response pattern that is predictive of the response in humans.

The controversy, whether animal trials were or were not predictive of human effects, developed in the EEG studies of opioids, their antagonists, and anticholinergic drugs. Abraham Wikler of Lexington saw that his dogs were restless, their legs moving continuously - they were studied in a sling - and yet their EEG rhythms were slow, similar to the rhythms of deep sleep. He deduced that the EEG findings, labeled 'sleep EEG', were different than the expected observed behavior or movement and concluded that the EEG effects of drugs

were 'dissociated' from their behavioral effects. His findings were corroborated by numerous authors studying rats, mice, dogs, and even monkeys.

In humans, opioids and anticholinergic drugs elicited specific EEG signatures. Slowing in the EEG was associated with sedation or delirium or stupor, which varied with speed of onset and degree, and increased alpha activity was associated with well-being, euphoria, relaxation, and so on. In addition to vigilance and motor activity, we could examine mood, thinking, memory, cognition, as well as task behavior of varying complexity. Such a variety of behaviors could be matched with a variety of EEG measures to produce an excellent theory of association between EEG and behavior.

Wikler's error was in assessing restless motor activity as the waking state, and in assessing slow waves in EEG as a sign of sleep. His animals were delirious, a state which he could not distinguish from restless sleep. But the damage was done. Wikler was the author of a respected textbook and a leader of his profession. He was very influential among the pharmacologists working in industrial laboratories. While many of the substances introduced in the 1950s had EEG analyses in animals in industrial laboratories, their failure to predict accurately led the research leaders to put aside such studies.

The human studies were better accepted in the 1970s and early 1980s, but with the increasing attention to the monoamine hypotheses, interest in human pharmaco-EEG waned. I know of no pharmaceutical laboratory or research director interested in pharmaco-EEG analyses today. Too bad, because our analyses of mianserin, doxepin, 6-azamianserin, flutroline, des-Tyr-gamma-endorphin, among many others, were much closer to the clinical mark than the pharmacologic assessments of these substances. The present drive to find the next substance affecting animal neurohumors can, at best, produce 'me-too' drugs, close or identical to existing compounds. There is no better than the state lottery chance to find a useful entity by the present philosophy.

If I may enter an aside, neurologists and psychiatrists ignore the EEG today. Psychiatric excitement is centered on PET, SPECT, MRI, functional MRI, and CT imaging. Putting aside the remarkable effectiveness of MRI and CT to localize brain lesions, what is the excitement for psychiatry? Researchers seek to localize the brain regions that control behavior, much like the cortical control of movement in the motor strip, and vision in the occipital regions. They ask patients to wiggle a finger, think a thought, or recall a memory, and then they look at the images to see what lights up. We have been through this type of work with EEG. The EEG changes in response to stimulation of any sense - evoked potentials, to motor movements, the bereitschaftpotential, anticipated activity - contingent negative variation, and vigilance - sleep EEG, sedation and sleep thresholds. It changes during periods when patients are hallucinating. The changes in such measures are related to the mental disorder, mood, hallucinations, imagery, and fantasy. EEG measures did not help us understand

psychopathology, but they did, and do, provide an ongoing measure, a moment-to-moment correlation of brain function with vigilance, mood, thought, sensory, and motor functions. Because they are immediately responsive, easily recorded, and easily quantifiable, they are much more sensitive to physiology than PET and SPECT scans, which only give 30 minute averages.

The structural image derived from EEG is not as sensitive as CT or MRI for anatomy, however, and I agree with neurologists that MRI and CT have replaced EEG for brain localization of structure. But for the functions that interest psychiatrists, it is too bad that quantitative EEG has been pushed into the background by the fancy equipment, which has excited such interest because it is "new". Further, I have yet to read a report on these new imaging measures in psychiatry with any theoretic foundation. Most observers seem excited to mount studies because of the Mount Everest effect. This is too bad. Modern EEG quantification methods have got far more powerful than the early ones we were using. They provide moment to moment numbers that are useful in studies of behavior. For example, we have come around to looking at the seizure EEG during ECT as a measure of an effective treatment, and the interseizure EEG as a measure of an effective course of treatment. So much so, that modern ECT devices have quantitative EEG scoring measures built in. Now that is an application that I and any psychiatrist can understand.

Quantification of the EEG was an important development. How did this come about?

Did you know that one of the first applications of computer methods at NIH was in sorting and measuring rating scale data? When the Psychopharmacology Service Center under Jonathan Cole organized the Congressional mandated research in new drugs, Dean Clyde and other psychologists taught us to use statistical methods. The first data set in which he used multivariate discriminant functions was that originated in the behavioral and EEG analyses of the Hillside Hospital chlorpromazine-placebo-imipramine study. We gave him the data and he cranked out the results on a university IBM system. In any case, Cole, Clyde, and others encouraged our interest in statistical analyses and that meant an interest in digital computer methods.

In 1957, George Ulett, a Professor in the Department of Psychiatry at Washington University, described the effects of atropine and scopolamine on ECT-induced EEG slowing. His findings paralleled my own. A few years earlier, George had read that the U.S. Government had declared surplus the material needed to build the Grey Walter electronic frequency analyzer, and he built such an analyzer for his EEG research. When I visited him in St. Louis, I saw the benefits of this device over hand measurements. I had to have one. A supplement request to NIMH provided the necessary $10,000 for George to build such a device for Hillside Hospital. That became the basis for our collaboration in pharmaco-EEG studies, and eventually for his invitation in 1962 for me to come to St. Louis to head his dream-child, the newly organized Missouri Institute

of Psychiatry. Frequency analysis became part of our EEG studies and was instrumental in discriminating drug effects. Indeed, it was the opportunity to use advanced methods of EEG analysis that drew me to the professorship at Washington University

In 1960, at the opening of the UCLA Neuropsychiatric Institute, MIT scientists demonstrated that it was possible to quantify changes in the EEG signal using a digital computer. The short epochs of EEG that were quantified were an exciting view of the future, which came quickly. Our association with the computer facilities at Washington University made possible a number of analysis programs - baseline cross, power spectral density, random shapes, and amplitude integration, each using an IBM 1620 computer at the Institute and the number crunching capacity of the University's IBM 7072. Slow and unwieldy, these programs required minutes to hours of crunching to analyze short segments of EEG. It was here that I teamed up with Donald Shapiro, then a graduate student in physics, who programmed our computer, and has been associated with my work and that of Turan Itil ever since. When I returned to New York in 1966, NIMH awarded almost $200,000 to develop the EEG analytic system using the IBM 1800 process computer, a mammoth device requiring its own room, special flooring, and 15-ton air conditioning units to keep its myriad transistors cool.

Such systems were used to analyze human EEG effects of drugs. With the increased speed of computer chips, it was possible by the mid-1980s to develop a very sophisticated EEG analysis system for $15,000. Since then, the sophistication has increased and the price come down so that a fine EEG analytic system is built into the latest ECT devices at an additional cost of about $1,000. This makes EEG analyses an integral part of modern ECT. Indeed, while EEG analysis has little place in psychopharmacology today, it is playing an increasing role in ECT treatment and research.

From where did support for pharmaco-EEG come?
Incidentally, little of US pharmaco-EEG research would have been possible had it not been for the encouragement and support of Jonathan Cole. Jonathan headed NIMH's Psychopharmacology Service Center. He was very eclectic, recognized the need for diverse studies, and leaned heavily to support human research. Others at NIMH thought such investment needed the secure underpinnings of laboratory research - what was then called 'basic' research - and discouraged human studies. As we saw in the 'association-dissociation' controversy, Jonathan's views were more productive than the efforts of laboratory scientists. NIMH supported many electrophysiologic studies, especially those of Charles Shagass, Turan Itil, and my laboratory. Support ended in the mid-1970s.

Much support also came from industry, both for laboratory electrophysiologic research and human studies. The laboratory support was mostly internal, the human research by contract with outside industry's sites.

In the early 1970s, it became possible to radiolabel receptors and see if your drug actually did bind to them and they began to look like the kind of target that magic bullets were there to hit. Do you think the rise of radio-labelling made the EEG seem less useful to pharmaceutical houses from the point of view of trying to produce new drugs?
I believe the situation was something like this. The managers of any pharmaceutical company have an unlimited supply of chemical compounds that warrant testing. First, the chemicals are sent for pharmacology and toxicity trials in animals. When they want to test more compounds than their present laboratory capacity can accommodate, they hire more technicians, rent or build more space, and buy test subjects from the unlimited supply of rats and mice. An assay takes a few weeks, at most. At the monthly research meetings, an endless supply of compounds are shown to have one effect or another, and each pharmacologist promotes his compound for the next phase of testing. What is known at the time is that the compound does not kill an animal immediately and that some measure has been affected, assumed to be predictive of a beneficial effect in man. In the same time that pharmacologists report on many compounds, the clinical director, who has the responsibility for the phase-1 and phase-2 human trials, can describe the assessment of only a few compounds, each assay taking many months. As the number of pharmaco-EEG contract facilities was always small, the number of substances tested was always much smaller than the number tested by pharmacology. Testing in the pharmaco-EEG model was too costly and took too long to get a clear answer, so it fell into disrepute - not for lack of success, but because of expense in dollars and time.

Another factor was the decision by NIMH committees in the 1970s to end governmental support for clinical psychopharmacology trials. Ostensibly as a result of the ballooning Vietnam War costs, research moneys were cut and the Early Clinical Drug Evaluation Units – the ECDEU system - the basis for the independent assessment of new drugs, fell by the wayside. Support for my pharmaco-EEG work ended in 1975. I was sustained for another six years by funding from New York State through the Long Island Research Institute, at the time headed by Stanley Yolles. But that support ended in early 1980s.

Turan Itil continued to do novel studies. After his success with mianserin, he tackled a number of hormones, some established and some novel, manufactured by Schering AG. He found identifiable EEG profiles, some meeting the profiles of known psychoactive groups, and some eliciting novel profiles. His suggestions that these compounds be tested in the clinic fell on deaf ears. The potential of this series of compounds has been ignored.

When you mentioned the Grey Walter frequency analyzer, I immediately thought about the debate in the 50s about whether the presence of neurotransmitters in the brain had anything to do with how the brain works. The electrophysiologists at the time, and he was prominent in this group,

felt that neurotransmission didn't have much to do with acetylcholine – that it was purely electrical.

The dominant philosophy in the 1940s and 1950s was that the brain was an electrophysiological organ. Such a view was encouraged by studies in electroshock, in EEG studies of psychopathological states, and in the many types of electrophysiologic signals, which could be elicited from the brain. Measurement of the average evoked response was made possible by the first Computer of Averaged Transients, a device built around 1960 by Manfred Clynes at Rockland State Hospital. Grey Walter developed the CNV- contingent negative variation - which he showed was an anticipatory response in the brain when the subject expected a signal. Grey Walter's work was very influential, especially his book *The Living Brain*, which projected a direct relationship between EEG signals and behavior. Grey made the Burden Neurological Institute in Bristol, England the Mecca for all electrophysiologists. His premature death in a motorcycle accident was a severe blow to the development of EEG. The ultimate blow was the development of chemical measures for brain neurohumors and the demonstration that Otto Loewi's Wasserstoff – acetylcholine - the neurotransmitter in the muscle synapse, could be found in brain tissues. The concept of the chemical neurotransmission quickly came to dominate pharmacologic thinking.

You mentioned Charlie Shagass, which raises the question of the role of personality and constitution, as well as the baseline level of brain function and how this influences response to drugs. He introduced the famous sedation threshold for instance.

Charles Shagass was another important figure in EEG research. Trained as a psychologist, then as a physician and electrophysiologist, he developed the sedation threshold, a measure of psychiatric diagnosis, for his M.D. thesis. He needed different doses of amobarbital to elicit the EEG fast frequency spindling activity, which characterizes the brain's response. Patients with organic psychoses, dementia, and depression required very little amobarbital, while schizophrenic and anxious patients often required as much as two to three times the dose for the same effect. "Normal' subjects showed an intermediate response. After visiting him in Montreal, I replicated his work. The sedation threshold is still a very good test, one that I still use in teaching, especially when I want to demonstrate the relationship between physiology and psychiatric diagnosis. Incidentally, since nystagmus is another sign of central barbiturate activity, I showed that we could identify the sedation threshold without EEG by checking for lateral nystagmus. He never forgave me for this observation, often reminding me that I had interfered with the proper use of EEG.

The sedation threshold is highest in chronic alcoholics. When I clinically evaluate a patient who has a syndrome that suggests alcoholism is a feature, and the patient denies its use, as many often do, I offer to do a sedation threshold. If they require very high doses to develop nystagmus, my diagnosis is secured.

Charlie's work complemented that of Ed Weinstein and Robert Kahn in their work on denial of illness. These authors showed that not only did the brain's electrophysiology change, but speech patterns changed as well. These provocative tests were, and I believe still are, the best physiologic classification measures of mental disorders.

Charlie went on to develop the sleep threshold - the amount of barbiturate that was required to induce sleep. He devoted most of his professional life to the averaged evoked response, publishing *Evoked Potentials in Psychiatry* in the early 1970s. In this work, he followed Eysenck's formulations of character pathology and sought EEG correlations. Unfortunately, his efforts failed, I think because he used averaged EEG signals rather than because of the EEG measure itself. Averaging destroys information, which could correlate with behavior. The relationship of EEG to behavior is immediate and variable. Averaging over many minutes loses this moment-to-moment correlation.

You asked about the relation of EEG effects of drugs and the starting or baseline condition. All the workers, not only Charlie, needed to relate the change in EEG to the baseline recording and we used the characteristics of the baseline, resting EEG as one of the factors in selecting volunteers for our pharmaco-EEG predictor studies. My experience with LSD is illuminating. In 1953, I described the effect of LSD on EEG in normal subjects and in unmedicated patients with psychoses, finding an increase in frequencies and a decrease in amplitudes, a shift to the fast frequency end of the EEG spectrum. But another investigator in Villajuif outside Paris, Pierre Borenstein, reported that LSD enhanced EEG alpha activity. This was an important discrepancy in findings. When I visited him in 1957, I found that he was working in a psychiatric hospital dedicated to patients with poorly controlled epilepsies. His patients exhibited continuous slow wave activity of high voltage, and LSD did, indeed, drive their frequencies to the fast end but starting from a very slow baseline, the overt finding was an increase in the EEG alpha (8-12 cps) frequencies. This work became the basis for our selecting both patients and volunteers with resting EEG patterns of high alpha activity for our drug studies.

Let me ask you this. One of the things you cannot ever show at the receptor level is a withdrawal effect of a drug. With the EEG you can show the effect of the drug on the whole system. Now if you read back through the neuroleptic literature in the 1960s many people had identified a neuroleptic withdrawal syndrome. Many of these people had a background in electrophysiology as did many of those who were involved in pointing up the withdrawal effects of benzodiazepines such as Ian Oswald and Malcolm Lader. Since we retreated from the EEG, do you think there has been a consequent loss of vision of what is happening the whole organism or person?

The EEG is a signal with moment-to-moment correlation to ongoing behavior. Eye-opening and eye-closure, for example, perturb the EEG immediately. As

does smoking a cigarette - within four to five puffs, the EEG shows a perturbation, which lasts for 20 to 60 seconds. That is why smoking requires repeated dosing. In subjects who have been dosed repeatedly, it takes many more puffs to elicit an EEG effect. This dosing and delay effect is evidence of tolerance. Take the amobarbital effect in chronic alcoholics. It requires very large doses of amobarbital to elicit the EEG barbiturate fast frequencies. Such data are interpreted as evidence of cross-tolerance of barbiturates and alcohol. The same was true when we gave opioid dependent subjects intravenous heroin. Those who were most dependent on heroin required larger doses of heroin, and often there was a delay in the EEG and in the behavioral high. After patients were detoxified, and we had allowed a week to go by, a much smaller dose of heroin elicited the EEG and the behavioral high. Incidentally, naloxone given intravenously will block the EEG effect of opioids within 30 seconds. The effect is immediate.

The enthusiasm about PET scans, brain chemistry, and behavior is, I believe, misplaced. The PET scan is another averaging system, seeking to measure brain activity over many minutes. Such averaging destroys the moment-to-moment information needed to assess relationships with mood and thought.

Can I take you through the evoked potential story and how it intersects if at all with quantitative EEG?

The averaged evoked potential (AEP) was a new instrument in 1960 and by 1963, we were studying the effects of drugs with the resting EEG and the AEP. One early study by Itil was to examine the effects of different doses and rates of administration of intravenous pentothal on EEG and AEP. The EEG measure was exquisitely sensitive, showing EEG frequency change within a minute. The AEP required at least 30 stimulations to show a change in AEP, and to get an image took about 5 minutes. We found the AEP insensitive to psychotropic drug effects.

You've outlined your early work with ECT but it then later became a subject of considerable controversy and you got involved in the middle of it – can you take me through this?

I have lived a good part of my life with ECT, first in research and as a clinician, then as an educator, and for the past two decades, as an educator, clinician, and advocate. When Meduna first injected camphor-in-oil into a catatonic schizophrenic, on January 24, 1934, he had a vision of an antagonism between epilepsy and the psychosis of dementia praecox. He derived his image, contrary to many disparaging reviewers, not from early uses of camphor but from neuropathological observations of the concentration of brain glia cells. There was a relative hyperintensity in epileptic patients and a paucity in those with dementia praecox. Clinicians' reports encouraged him. When psychotic patients developed seizures, as after a head injury or encephalitis, their psychosis ameliorated. His work was quickly replicated and by 1936, it was hailed as an effective treatment. The Italians developed an electrical induction method in

1938, and by 1940, electroshock was widely accepted throughout the world as the principal treatment for psychosis, depression, and mania. Until the introduction of chlorpromazine and imipramine in the mid-1950s, ECT was the principal treatment for the mentally ill. It was widely practiced in state and academic hospitals, and in offices, throughout the world.

With our first experiences with the new psychotropic drugs, many of us believed that they were as effective as ECT, lobotomy, and insulin coma, and since they were much easier to administer and seemingly less expensive, the drugs quickly replaced these treatments. Sadly, by the early 1970s, we recognized therapy-resistance to the medicines, and even with augmentation and drug combination strategies, we often failed to help our patients. What were we to do with persistently psychotic, manic, and depressed patients that required so much attention? For some practitioners, with experience in ECT, the answer was to recall its use.

It was an unfortunate time to recall the treatment. The Vietnam War had brought the public into direct conflict with governmental authority. The conscription of men for an undeclared and a perceived illegal war led to protests, many violent, and a national outcry against irresponsible authority. Popular authors, like Thomas Szasz, argued that the state had no right to incarcerate a patient or treat one against his will. The Church of Scientology, a popular anti-authority movement, chose psychiatry, and especially ECT, as its target. And, within the professions, psychoanalysts, psychologists, nurse practitioners, and even clergymen, seeking to establish footholds in what seemed the lucrative business of psychotherapy, used ECT as a scapegoat. Hollywood got into the act in 1975 with *One Flew Over the Cuckoo's Nest*, a very successful and powerful argument against electroshock and lobotomy. By 1972, in response to these public outcries, legislators promulgated laws that made ECT illegal. The most egregious example was in California. Practitioners appealed to the courts, and the outright ban against the use of ECT was enjoined. The legislature came back with onerous restrictions on the use of ECT, restrictions that are still a feature of practice in California in 1998.

In Massachusetts, the same legislative forces were deflected by the Mental Health Commissioner, Milton Greenblatt, who established a task force to study the proper role of ECT. The task force found many reasons to sustain the use of ECT, but noting records of abuses in its use, recommended regulations regarding consent for its use.

Psychiatrists in California appealed to the American Psychiatric Association for advice on how to respond to the legislation and the APA established a task force to provide guidelines for the proper use of ECT. I was selected as a member of the task force, mainly because I had organized a meeting on the mechanism of action of ECT in 1972. The task force met over three years, publishing a report in 1978. That report found ECT to be an effective treatment for some mental

disorders - in many instances more effective than drugs, that it was often life-saving, and that it was safe. But consent was an important issue, and for the first time, formal consent procedures for the use of ECT were recommended. The report also described the proper use of ECT. The report was accepted as the basis for the re-establishment of ECT treatment facilities.

My impression is that this wasn't a world argument, it was a U.S. argument, although in some European countries such as Holland things were also a problem.

Not so, the antipathy to ECT was worldwide, and remains so today. At present ECT has a very patchy application in the world. In Germany, Japan, and Italy, ECT use is very limited. In Germany, it is available for a few patients in some academic centers. In Italy, it is available in only a few private sanitaria. My image is that if your physician has a contact, you may be referred for ECT, something like the abortion situation in this country before Roe vs Wade. In Japan, the students revolted against academic and professional authority to such an extent that no academic center acknowledges the use, or even the awareness, of ECT. Similar attitudes restrict the use in Holland.

ECT has been sustained in Scandinavian countries, and indeed, much research was done there during the 1950s and 1960s. ECT has also been sustained in Great Britain, Ireland, Australia, New Zealand, and Canada. But it is undervalued in these countries and except for the spate of ECT and sham ECT research in the late 1970s, little academic interest exists. Incidentally, the ECT and sham ECT research was encouraged by the doubts of the efficacy of ECT by the gadfly psychologist Timothy Crow. He wrote a damning essay, published by Michael Shepherd in Psychological Medicine*,* arguing that ECT was a traumatic placebo without specificity and benefit. In response, the MRC supported studies of ECT and sham ECT that again showed that ECT was an effective agent. In some Third-World countries, such as Nigeria, South Africa, India, and China, ECT is widely used, mainly because it is effective and inexpensive. In these countries, unmodified ECT, without anesthesia is the standard method of treatment, much as ECT was done before the 1950s. In the former Soviet Union and East-European countries, ECT has some use, but here, too, the descriptions are of the general use of unmodified ECT.

What has been your role in all this?

Although I had broad training in neurology, psychiatry, and psychoanalysis, two topics interested me the most, the changes in EEG which occurred with psychotropic drugs and with electroshock, and the remarkable clinical benefits of ECT. We have discussed the EEG story.

My interest in EEG had its roots in the studies of ECT and insulin coma, two treatments that have dramatic and persistent effects on the EEG. That it was necessary to elicit increased slowing of the EEG frequencies for clinical improvement gave me great respect for the EEG as a measure of the changes in

human behavior. ECT alters the EEG dramatically, while the changes associated with psychoactive drugs were much more subtle. Indeed, we had to develop sophisticated digital computer analytic methods to measure drug effects.

Like many others, I thought that psychoactive drugs could replace ECT, much as they had replaced insulin coma. While I was in Missouri, between 1962 and 1966, I had no interest in ECT. But in 1966 I returned to New York to study drugs of dependence at the New York Medical College. A psychiatric resident, Richard Abrams, asked me to sponsor a study of unilateral ECT and of multiple monitored ECT (MMECT), two new techniques which promised to change ECT practice. With a grant award from the NIMH, we found that unilateral ECT was, indeed, an effective treatment that impaired memory much less than did bilateral ECT. But it was also less effective. Its benefits were less secure than those of bilateral ECT. The patients often required more treatments to obtain the same degree of clinical benefit. The EEG changes induced by unilateral ECT were also less in degree than that of bilateral ECT, and often were lateralized, not affecting both hemispheres equally. Perhaps this lack of bilateral brain change was the basis for the lesser efficacy of unilateral ECT. We found MMECT to be no better than single ECT, with the added risk of delirium and persistent dementia, and we strongly recommended that MMECT be discarded.

At a time when few scientists were looking at this treatment, I was invited by Milton Greenblatt to edit a number of Seminars in Psychiatry. This appeared in 1972. At the same time, NIMH asked that I organize a conference on ECT mechanisms. With the collaboration of Seymour Kety of Harvard and James McGaugh of UC-Irvine, we called together groups of researchers, most with preclinical experience with electroconvulsive shock, to discuss three possible mechanisms of ECT action - neurohumoral, memory, and electrophysiologic theories. The conference was held at the Dorado Beach Hotel in San Juan in April 1972 and the proceedings were published as The Psychobiology of Convulsive Therapy. While it provided few conclusions, it did bring together clinicians and laboratory scientists, who left the sessions with a greater appreciation of the powerful and diverse effects of ECT.

In 1972, I moved to SUNY at Stony Brook, and did little in ECT for the next few years. As the public attacks on ECT became more raucous, however, with legislative actions proscribing its use, I was appointed as a member of the American Psychiatric Association Task Force on ECT. Asked to review the indications and the research issues for the report, I became intrigued by its broad effects, which contrasted sharply with the focused and limited effects of psychoactive drugs. The report appeared in 1978. Because the report was limited in scope, it seemed timely to bring out a new textbook, one that would be more than a compendium of clinical opinions and practical advice. During a sabbatical year, I wrote Convulsive Therapy: Theory and Practice. It was published by Raven Press in 1979. It was well accepted and was the standard text until it was replaced by Richard Abrams' textbook in 1988.

When University Hospital opened an adult in-patient unit in 1980, I turned to organizing an ECT Service, and for the next 18 years used the service for research and teaching. The early years were quite stormy for ECT, despite a broad acceptance of the APA report that was the basis for establishing many ECT programs.

In 1984, I was invited by Ole Rafaelson to give the plenary talk on ECT at the meeting of the CINP in Florence. It was a magnificent hall, and the audience was duly appreciative. At the end of that day, Alan Edelson, publisher of Raven Press, invited me to dinner and offered me the opportunity to establish a journal. Despite its limited audience, he encouraged me to consider the topic of ECT and in 1985 we launched Convulsive Therapy, a quarterly scientific journal. I edited it until 1994. It soon became the official journal of the Association for Convulsive Therapy, a society which Richard Abrams and I had revitalized as a scientific body. One of my coups as editor was to track down Meduna's autobiography. I edited and published it in Convulsive Therapy. My experience allowed me to write a well documented history of convulsive therapy for the 50th anniversary in 1984, and to memorialize the introduction of ECT in a special number in 1988.

In 1986, Richard D'Alli, then a science reporter on KAET in Phoenix, and now a child and adolescent psychiatrist on the staff of Johns Hopkins Medical School, and I produced two videotapes on ECT, one for professionals and another for patients and their families. These are still in print. To round out the services for patients and their families, a few years ago I began work on a trade book on electroshock, a project which interested Oxford University Press. The book is in press, and will appear in the spring of 1999, titled Restoring the Mind: The Promise of Electroshock. With that work, I have completed an extensive library of educational materials - textbook, scientific journal, histories, videotapes, and a trade book, in addition to more than 250 scientific papers and numerous lectures throughout the world on ECT.

Why do all this? Well, attacks on ECT continued throughout the period, with negative images in films, on TV, in talk shows, and in the press. Noisy protests often occurred at meetings, and demonstrators protested my talks, marching in the halls with hostile placards. At one meeting, I was handed a skillet with a cow's brain, covered with many dollar bills, by an angry demonstrator. At another time, in Rome, placards proclaimed: "Fink, take your videotape back to the idiots in America."

In 1985, NIH organized a national consensus conference with a full day of hostile presentations. The panel endorsed the continued use of ECT for some mental disorders, and recommended that further educational and research efforts be undertaken. This publication, published in JAMA, did much to encourage some acceptance of ECT within the medical profession. In the same year, Sidney Malitz and Harold Sackheim of Columbia University organized a conference on

the mechanisms of action of ECT. This meeting, too, had loud public protests that interrupted the sessions.

But despite these public attacks, the public image of electroshock slowly became less harsh, and in the next few years articles remarking on the revival of interest in ECT appeared in the public press. Professional training opportunities expanded, and governmental support encouraged detailed research on the physiology of ECT at Columbia and Duke Universities - the effects of different currents, energies, and electrode placements on clinical outcome, cognitive tests, and EEG. The technical problems in treating patients with systemic diseases were successfully tackled and by 1990, we had become so sophisticated that the list of conditions for which ECT was contraindicated had shrunk considerably. The changes in practice encouraged the American Psychiatric Association to establish a second Task Force and its report in 1990 became the standard for U.S. practice.

In the next years, attention was directed to the irksome problem of early relapse after a successful course of ECT. Many doctors assumed that the benefits of ECT could be sustained by continuing pharmacotherapy. Not so, for patients who came to ECT after having failed multiple trials of medicines, these medicines were no more effective after ECT than they were before. Two multi-hospital collaborative studies of continuation treatments and ECT were supported by NIMH. One was under the leadership of Harold Sackheim, in sites at Columbia University, University of Pittsburgh, and the Carrier Clinic in New Jersey. Patients with unipolar depression, who respond to an index course of ECT, are randomly assigned to continuation nortriptyline, nortriptyline combined with lithium, or placebo. The second study, under the leadership of Charles Kellner of the Medical University of South Carolina, has sites at Long Island Jewish, Hillside Hospital in New York, the Mayo Clinic in Rochester, and the Southwestern University of Texas in Dallas. This group is comparing continuation treatment with lithium and nortriptyline, in the same dosing schedule, with continuation ECT. I am the principal investigator at the Hillside Hospital site.

ECT's role in clinical practice has changed. First came the awareness that ECT is both very effective, and when properly done, very safe. Managed care insurance demands the use of the most efficient treatments, and comparisons of ECT and medications are repeatedly finding ECT the more economic, as well as more effective, treatment. There is a grudging, but increasing, interest in ECT, with more and more psychiatrists seeking training and establishing treatment facilities throughout the nation. I established a CME training program in ECT at Hillside Hospital early in 1998, and we certificate practitioners after five intensive days of hands-on and didactic experience.

How do you see the role of ECT today?
Convulsive therapy was introduced as a treatment for patients with dementia praecox. Within a few years, its efficacy in relieving mania and depression was

recognized, and in the ensuing years, its effects in relieving catatonia, parkinsonism, and the neuroleptic malignant syndrome were described. Overall, ECT is a very effective treatment for patients with mental disorders, those who are ill enough to warrant hospital care. We recognize two sets of indications, primary and secondary. The primary indications, those patients who may be recommended for ECT even without a prior medication trial, are those who are severely suicidal, manic and excited, or suffering from inanition, such that they require continuous observation or restraint. The secondary indications are more common -- depressed, manic, psychotic, and catatonic patients who have failed medication trials. Depressed elderly are a commonly treated group, since many are intolerant or unresponsive to medicines.

You mentioned a specific role for ECT in catatonia. How did you come to that conclusion?

Although I had been an active participant in the American Psychopathological Association, and even became its President in 1973, I had made no important contribution outside the classification of medicines and the description of drug-induced mental states. In 1984, I became interested in the neuroleptic malignant syndrome (NMS), when I made the diagnosis in three cases in a few months at University Hospital. We treated two patients symptomatically, but the third looked like a candidate for ECT, and after a short course, he responded dramatically. We published these cases in one of the early confirmations of the syndrome.

In 1987, I saw a young woman who was mute, rigid, feverish, with autonomic instability and a markedly elevated CPK. She had come to the Emergency Room in a manic delirium, was given haloperidol, which elicited a seizure, and thereafter the full-blown syndrome of NMS. The cause of her excitement was diagnosed as lupus cerebritis, and while the internists fussed with systemic drugs, the psychiatrists pumped her full of anticonvulsants and sedatives. After seven weeks of mutism and stupor alternating with excitement requiring restraints, she was referred for ECT, and with two weeks of treatment, the mental syndrome abated. The family and internists, fearing long-term memory effects, insisted we stop ECT, over my objections. She relapsed, and a few weeks later, I was able to give her a proper course of ECT. She recovered.

There was an interesting sideline on this. Because she was on very high doses of anticonvulsants and benzodiazepines, I was unable to elicit an adequate seizure in the first treatment. I went to my laboratory, brought out some Metrazol, and was able to elicit a good treatment with Metrazol and ECT. The spirit of convulsive therapy is not inherent in any aspect of the electricity, but in the brain changes occasioned by the seizure.

Since that time, I have encouraged studies of catatonia - NMS is a type of catatonia. We developed a rating scale for catatonia, applied it over six months in admissions to University Hospital, finding that 9% of admissions exhibited at least two formal signs of catatonia. Indeed, catatonia is not as rare as many have

thought, nor does its presence signify schizophrenia, as the DSM and ICD classifications assert. Because it appears more often among patients diagnosed as manic and depressive, I was instrumental in getting the DSM-IV task force to include a category of "catatonia secondary to a medical disorder" for such cases.

The study of catatonia has made me aware of the importance of diagnosis in treatment. Because catatonia has been defined as a type of schizophrenia, most psychopharmacologists and texts use antipsychotic medications for the condition. That is too bad, first because they are not very effective, and because in some patients, they elicit NMS by worsening catatonia. The best treatment for catatonia is a sedative anticonvulsant drug like a barbiturate or a benzodiazepine. But these medicines must be used in high doses. When they fail, ECT is the ultimate, almost 100% successful treatment. I am often asked why not use it first line. My answer is that I do but psychiatrists' allegiance to the flag of pharmacology compels the use of medicines first.

Such experience led me to re-examine the role of ECT in schizophrenia. A literature review showed that in the early studies of chlorpromazine and ECT, both were found equivalent in potency, and here, again, as with insulin coma, medications were easier to administer and less expensive. But medications often fail. At the best of times, neuroleptic drugs are 60% effective, leaving a large number of patients severely ill. It is at such times that ECT comes into its own. It remains the ultimate effective treatment for schizophrenia. We have been able to dissect the types of syndromes for which it is effective, and these are best described as those with positive symptoms, the paranoid and catatonic subtypes. ECT, like neuroleptics, is not very effective in the schizophrenic syndromes dominated by negative symptoms. Indeed, I often recommend ECT as the initial treatment for the acutely psychotic patient during their first psychotic episode. I especially recommend ECT for college students who have their first psychotic break, whether occasioned by the stresses of leaving home or the abuse of drugs. It seems silly to me to offer neuroleptic drugs, with their risks of tardive dyskinesia, parkinsonism, and NMS, their 60% success rates, and the long periods of administration which are required compared to the immediate efficacy of ECT, with a relief of psychosis within three to four weeks.

How if at all do ECT and psychopharmacology relate?

Modern psychopharmacology is divorced from electroshock in its clinical practice, training, and research. None of the leaders of the ACNP, the ECNP, the Society for Biological Psychiatry, and since the death of Ole Rafaelson, none of the leaders of the CINP, have any interest in the effect of seizures on brain functions, brain chemistry, or behavior. Almost all admit that ECT is a useful option, adding the caveat, 'after all medication options have failed'. The 'after all medication options' usually includes standard medication trials of 4 to 8 weeks each, augmentation trials, combination trials, and with the announcement of any new entity, experimental trials with it. That is too bad, since an opportunity to help patients quickly and effectively is ignored.

From a research standpoint, the lack of interest is even more egregious, since the opportunity to learn about brain mechanisms is neglected. ECT's remarkable breadth of action, even after the failure of the best selected of modern medicines, should encourage such interest. Consider the unique actions of ECT - it relieves depression, mania, psychosis, and catatonia, each in a variety of its forms. That a single agent is more effective than any other treatment for mental disorders - including the latest psychoactive drugs - should encourage an interest in its mechanism. Unfortunately, our leaders are prisoners of the belief that brain neurohumors are the site of mental illnesses and their relief. They look upon electroshock as a 'dirty' intervention; it has too many effects to be understood. Many quote Seymour Kety's 1972 aside that electroshock affects too many brain systems ever to be understood. Rather than shun it, investigators should be seeking to understand its mechanisms. I see two important questions that will be better understood by studies of ECT - one is the classification of mental disorders and the second, it will reinvigorate our interest in the endocrine aspects of brain functions.

We view depression, manic depressive illnesses, schizophrenia, parkinsonism, and the neuroleptic malignant syndrome as individual entities with different pathologies. Some focus their interest on different genetic roots. But consider the possibility that these disorders are different expressions of a common pathophysiology. What has been termed a "unitary disorder". Such an opinion is not so far-fetched as it seems when first stated. Consider the analogy of neurosyphilis, the 'great imitator'. The same infection of the central nervous system is expressed as paranoia, depression, mania, dementia, delirium, and tabes. These different behavioral syndromes are separate entities in DSM-IV. Yet, in neurosyphilis, each syndrome arises from a single cause. Its onset may be slow, but often acute. It has different systemic manifestations, but its course, like that of schizophrenia, is relentless. Had penicillin been discovered before the Wasserman test and the identification of the spirochaete assured accurate diagnosis of the infection, would penicillin's efficacy in relieving these diverse syndromes not have encouraged some clinicians to consider that each syndrome might have had a single, common cause? The broad effectiveness of ECT should be a caution to the DSM and ICD Kraeplinologists, who continue to propose Chinese-menu typologies of symptoms and life history as the basis for the classification of disorders and as the basis for their search for new medications.

Studies of electroshock suggest a different view of brain functions. We can look at the brain, not only as an organ whose cells communicate across synapses by the transfer of neurohumors but as an endocrine organ. The brain produces many peptides and other chemical messenger substances that are distributed throughout the brain by the CSF system, and which pass to the blood stream to bathe all the body's tissues. These messenger substances modulate vigilance, sleep, and waking; mood, memory, and thought; sexual interest; growth and

senescence and even death. In contrast to the neurohumors which affect a few cells locally, and do so for milliseconds, endocrine products have effects for hours, modulating all bodily processes, often at distant sites from their source. I envision a single systemic cause for depression, for example, possibly, a decrease in a hypothalamic peptide that controls mood. If its production is disturbed, a disorder with depressed mood, and loss of energy, concentration, appetite, and sleep results. Seizures, as in ECT, elicit an abundant release of the peptide, and even re-establish a more normal metabolism in response to repeated stimulation. The model is best seen in our knowledge of diabetes, a deficiency of the production of insulin by pancreatic cells. Diabetes affects all systems of the body. The consequences of this deficiency vary with the age and development of the host at the time the deficiency is manifest. The same is true for deficiencies in thyroxin.

And, while I have pictured a deficiency of hormone as the basis for diabetes and hypothyroidism, we have instances of the widespread consequences of over-production of hormones. So it is possible that my image is incorrect, that it is not a deficiency of a peptide that causes depressions, but an overproduction. Either case compels consideration of the brain's endocrine functions and endocrine products. Despite our excited interest in biochemical genetics, neurohumors, receptors, and brain imaging, there is little likelihood that these disciplines will do much to improve our knowledge. What little these disciplines have added, has already become manifest, and while the medicines are often useful, there is still much more that needs to be known and done. In our present pre-occupation with neurohumors and receptors, I am reminded of the pointed story of the drunk who is groping around a lighted lamp-post. Queried by the second drunk, he says that he lost his keys. The second drunk also looks around and after frustrating minutes, asks whether the first had reason to believe he had lost his keys around the lamp-post. The first answered, no, he had lost his keys elsewhere. "Why look here, then?" "Because this is where the light is."

We search for the relationships of neurohumors and receptors to mental illness because we have the technology for such a search, because we believe that animal systems are the same as systems in man, and because animal studies are inexpensive. We have no reason to believe that the mental disorders, that we seek to ameliorate, arise from such mechanisms. Neuroendocrine research is more difficult, and logically it must be done in humans. It deserves more attention and my views of electroshock encourage such a change in attitude.

Are you and ECT in a similar position to Mogens Schou and lithium in that you both have a treatment that works but neither of you have the market development powers of a large pharmaceutical company behind you. You've had to create all the science yourselves and a few key people have kept the whole show on the road.

Mogens Schou was lionized by the profession. There is not a single figure in ECT that is so lionized. At this moment in history, I am probably the leading advocate and student of electroshock and believe me I have not been lionized.

But are you in the same position in the sense that you need a pharmaceutical house behind you for these things to take off?
No, we do not need the support of a pharmaceutical house, surely not with their present disregard for researchers, where companies define the questions by their support, where they insist on writing the protocols, and where company people even write the published reports. No, to develop a greater awareness of ECT, we do not need the support of industry. What is needed is public awareness of the benefits of electroshock, its safety, and that it works when all medicines fail. What favored Schou's image was that lithium therapy worked.

But once he dies, will lithium go with him?
Well, lithium is now in a tougher position because of the hoopla about Divalproex, a substance with limited benefit. It is pushed by a pharmaceutical house and its shills. Lithium will remain in use because it is effective.

That's the difference. The pharmaceutical house distribute the literature through their detail men etc
Yes, that is part of the truth. The rest is the direct payments to the researchers for their research and their lectures at meetings. ECT does not have that. But lithium is a fine medicine, and it does not have the same negative connotation that ECT has for the public and the profession.

No, I'm not saying that it does but you are both in the situation where no large corporation feels that they can make money out it and therefore at this APA meeting you're not going to have the glossy exhibit stand. You can't buy hearts and mind with little pens and diaries and meals – you don't have the trinkets to get the natives to hand over Manhattan to you.
True. There is one thing on our side. ECT works. At present, less than 8% of members of the APA say that their practice includes ECT. That means that 92% do not use it, and are probably ignorant of its benefits or risks, their knowledge being no better than that of laymen. In the past 30 years, since the introduction of lithium, we have not seen a new entity come to clinical use with a spectrum of activity that differs from that existed before 1965. Perhaps you will argue that clozapine has a unique profile, and I may well agree. But other new entities are 'me too' substances. Some have better side-effect profiles, but their efficacy and specificity is hardly better. No new substance is effective to the degree, with the assurance, and with the security of ECT.

Public awareness of these benefits improves gradually. There are more than 900 subscribers to JECT, the successor name to Convulsive Therapy, and the Association for Convulsive Therapy has more than 300 members. We seek an ECT certification procedure for our practitioners, hoping to avoid what has

happened in Great Britain. The British are discovering that the 1981 report of Pippard and Ellam, the report that Lancet labeled a shame on the profession, has had little effect on practice. Pippard's follow-up studies on practice and the recent reports of lack of training of registrars in ECT are disappointing. The fact that the head of the British task force on ECT is a psychoanalyst is probably a factor. Such a continuing appointment is best interpreted as evidence of a disdain with which the Royal College holds ECT.

The future of ECT depends on some unusual forces. The growing recognition of its efficacy and its safety are a plus. As is the recognition that the death rate is very low, at the same level as normal pregnancies in the West. The frustration of our patients is another factor, for many are now turning to the Internet for advice, and while they find many negative diatribes, there are some good sites describing the treatment in positive terms. Many residency programs include ECT as a useful part of the curriculum. CME courses in ECT continue to develop. We began an intensive 5-day practicum at Hillside Hospital early in 1998, and the subscriptions continue to come in. We provide ECT five mornings a week, with more than 50% of the treatments in out-patients. Finally, managed care insurers are having an impact. While it is reasonable to give a newly ill patient a favored psychoactive medication, and to try a second if that fails, the time will come when psychopharmacologists will no longer be free to interminably prescribe one 'me, too' medicine after another. At some point, probably after two 6 week trials of medicines of different classes have failed, they will be required to consider the possible merits of ECT.

The main advantage of ECT, the advantage that sustains its use, is its efficacy for severe mental disorders. It is more effective than the alternatives, and it's present practice is safe in the hands of knowledgeable practitioners. Electroshock will be used because it works.

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