

## W. Edwin Fann: A History of The Tennessee Neuropsychiatric Institute

### Zueignung

Und mich ergreift ein längst erwöhntes sehnen  
 Nach jenem stillen, ernsten Geisterreich,  
 Es schwebet nun in unbestimmten Tönen  
 Mein lispelnd Lied, der Äolscharfe gleich,  
 Ein Schauer fast mich, Träne folgt den Tränen,  
 Das strenge Herz, es fühlt sich mild und weich;  
 Was ich besitze, seh ich wie im Weiten,  
 Und was verschwind, wird mir zu  
 Wirklichkeiten.

Goethe. *Faust*

### Dedication

I am seized by long forgotten yearning  
 For that kingdom of spirits, still and grave  
 To flowing songs I see my feelings turning,  
 As from Aeolian harps, wave upon wave;  
 A shudder grips me, tear on tear falls  
 burning,  
 Soft grows my heart, once so severe and  
 brave;  
 What I possess seems far away to me,  
 And what is gone becomes reality.

Goethe. *Faust*;

--translation by Walter Kaufmann

The quote from Goethe is in tribute to Fridolin Sulser, my German-speaking mentor and boss at TNI, who oft-quoted Goethe, and gave me my first copy of Goethe's *Faust*.

The Tennessee Neuropsychiatric Institute (TNI) was conceived in the early 1960s and fostered by Dr. Allan Bass, the great Chairman of Pharmacology at Vanderbilt University Medical School, who began seeking funding for the Center. The concept of a psychopharmacological research institute affiliated with a medical school was gaining currency nationally and had attracted interest of a prime mover, Daniel Efron, at NIH. The concept also attracted national attention from mental health cognoscenti as Psychiatry began a slow turn away from the then regnant Freudian Psychoanalysis to a scientific base and medications were becoming increasingly important in the Specialty.

Jim Dingell, who had been brought to VU by Pharmacologist Milton Bush, joined Dr. Bass' planning process that was aided and abetted by the hands-on encouragement of Daniel Efron. Frank Luton, a senior and highly respected psychiatrist (later Commissioner of Mental Health) in the Tennessee Department of Mental Health, gave strong support to the project. He militated for placing the Institute at the Nashville's Central State Psychiatric Hospital (CSH) for the salutary effect he believed it would have on that institution. Wherein Vanderbilt Psychiatry had over the years given only minimal attention to CSH, Bass also trusted that TNI's presence on the hospital campus would be a supplementary benefit to the treatment programs at CSH. Jim Dingell did much of the writing of the proposal and Efron guided it through the Washington maze. As planned, TNI would be faithful to Dr. Bass' conceit of having basic and clinical scientists working synergistically in close proximity under the same roof.

To develop the Center Bass forged a unique tri-partite funding structure for his project. The federal grant was the foundation of the enterprise. Then, with Frank Luton's leadership within the Tennessee Department of Mental Health, he persuaded that agency to allow the three-story Cooper Building at CSH in Nashville to be converted to laboratory space and a clinical research ward. The State also funded a secretary, laboratory equipment and a research psychiatry position. CSH was 10 miles from the main Vanderbilt campus with both advantages (and disadvantages) of such a remove. In addition to the basic scientist positions, two additional psychiatrist positions were funded by the federal grant. Vanderbilt rounded out the tri-partite model through contributing private funds.

Dr. Bass began with the easy part for him: having built the Country's number one Department of Pharmacology, with outstanding scientists in several other specialty areas of Pharmacology, it was relatively easy for him to attract top-flight basic psychopharmacologists to Vanderbilt. The first two floors of the Cooper Building at CSH were dedicated to laboratories. James Dingell in Drug Metabolism, became the first to set up operations in the then-dreary surrounds of the Cooper Building. Floris deBalbian Verster in cholinergic, psychologist Jack Tapp and Hans Dieter-Detbarn followed. For the Director of TNI, Bass recruited the charismatic Fridolin Sulser from The Burroughs-Wellcome Co. When Tapp departed for another setting, the pre-eminent psychologist-psychopharmacologist Oakley S. Ray filled his position, a most fortunate addition. The basic science group's early research interests were centered principally on elucidating the pharmacology of amphetamine; the role of norepinephrine and other adrenergic

agents (acetyl-choline, serotonin) in the pharmacology of tricyclic antidepressants and other psychotropic agents were also a major focus of their work.

By 1967, the basic scientists at TNI were actively conducting research and publishing their work in major reviewed scientific journals. Developing the Clinical Division of TNI, however, was to become more problematic for Dr. Bass. From the beginning, Vanderbilt's long-time Chairman of Psychiatry, William F. Orr, a psychoanalyst, refused to cooperate with Bass, averring repeatedly that research involving patients was "inhumane." Consequently, Bass was left on his own in this matter, but was able, through his colleagues and professional contacts, to acquire a candidate roster of nationally-ranked psychiatrist investigators. Among the established clinical psycho-pharmacologists who visited were Arthur J. Prange from Chapel Hill, N.C, Kanellos Charalampous from Houston and several candidates from NIMH. All were reportedly favorably impressed and intrigued by the TNI concept, the existing facilities and the basic scientists already at work there. They all politely declined, however, understandably not wanting to leave their excellent and established surroundings to assume the daunting task of developing a Clinical Division facility from scratch. In 1964, in a real *coup*, Bass had brought in John A. Oates, who rapidly developed Clinical Pharmacology at Vanderbilt University Hospital into the premier group it continues to be. While each candidate gave cognizance to the presence and clinical support of Oates' group, the lack of support from Psychiatry was reportedly a determining factor in their decision to decline.

In the meantime, I was completing my two years of obligated service at the Nashville VA Hospital. I had come to know Dr. Bass through attending Departmental seminars and knew of his national reputation in Pharmacology. I was Board Certified in Psychiatry, but had no formal research training, other than conducting a required project during residency and assisting John Griffith in his opioid and amphetamine research at the VA. I had ample experience with psychotropic drugs, however, and was aware of their growing importance in the future of Psychiatry. I was also very mindful of their therapeutic limitations and their damaging side-effects. From what I was hearing of Dr. Bass' plans, the possibility of working and training in such an outstanding group seemed a perfect and exciting career change for me. I approached Dr. Bass about the clinical position. After he discussed my candidacy with all concerned, including the new Commissioner of Mental Health, Nat Winston, I was selected to fill the first clinical position. Because of my lack of experience and formal training, however, I was made Acting Director of

the Clinical Division of TNI with the proviso that a more senior, tenured Director would be appointed later. The Psychiatry Chairman, Orr, showed his displeasure at my joining the group by taking away my psychiatry office. After that I had to borrow space in which to evaluate and treat patients.

Having suffered through the unnecessary delay in opening the Clinical Division, Dr. Bass and everyone else were anxious to get things under way. There was not undue pressure but I was given multiple tasks for my new position. The first priority was to get some clinical research going, which would have to be performed not at TNI, but off-site at VUMC. For this I had to obtain local Hospital and Medical School approval for the several protocols, identify suitable research subjects, admit the research volunteer-patients to Vanderbilt University Hospital and begin the actual work of the research. I oscillated between VUMC Research Center and working with State personnel at CSH designing the Cooper Building Ward and preparing contracts for the work to be done. There was also continuing national search to fill the other two clinical positions. I borrowed space in Fridolin Sulser's lab, obtained an Investigational New Drug permit for lithium and began a lithium research and treatment clinic at TNI. Dr. Luton facilitated my staff appointment at CSH so that the Hospital Pharmacist could make and issue the lithium capsules to our patients on my prescription. My very able technician drew blood samples and performed serum lithium determinations with a flame-photometer. A roster of bi-polar patients quickly accrued from the Vanderbilt catchment area, some of which volunteered as research subjects. Since there were no clinical research facilities at TNI, I strengthened my relationship with John Oates, who readily accepted me into his excellent group at VU Hospital. Through this relationship I was afforded access to the VUH Clinical Research Unit, laboratories and research nurses and assistants and, importantly, clinical consultation for my patients.

Thanks to the beneficence and tutoring of John Oates and his staff, I began a number of projects exploring the pharmacology of antidepressants and antipsychotics in man, using their effects on the peripheral adrenergic neuron as a surrogate for the then-inaccessible central neuron. I borrowed methods developed by one of Oates' Fellows, Jerry Mitchell. Mitchell, in his hypertension research, used blood pressure responses to the infused indirect adrenergic agent, tyramine and, using the Harvard Pump, the direct adrenergic agent norepinephrine. Serial BP readings were measured before and after administration of the test medication. The results from these methods revealed effects of the test medication on the peripheral pre- and/or post-synaptic

adrenergic neurons. The results correlated precisely with data from the effects of these drugs on animal CNS and peripheral neurons. These data led us to believe that the peripheral neuron was a valid model for clarifying some of the pharmacology of newer antidepressants in man. We performed pre-marketing studies of doxepin and iprindole, showing some unique pharmacology of these agents compared to marketed antidepressants; doxepin possessed some post-synaptic blocking effects and iprindole, uniquely, showed no pre-synaptic uptake blocking. This model was also used to explicate some of the pharmacology of lithium.

John Griffith, a VU psychiatrist, also began working within Oates' group to expand his ground-breaking clinical studies of amphetamine-induced psychosis. Griffith was very supportive of the Clinical Division's development and I, reciprocally, assisted Griffith in his studies of volunteer amphetamine addicts admitted to the VUMC CRU. Amphetamine as a cause of psychosis had not been, at that time, an established or accepted fact in all quarters. Giving carefully titrated doses of oral amphetamine, Griffith was able to demonstrate, through meticulous, repeated testing, the incipient signs of psychosis, and that these signs would quickly abate with cessation of the amphetamine dosing. As a corollary of these studies, Griffith, working with Jim Dingell and Fridolin Sulser at TNI, demonstrated in hospitalized addicts who had taken very large doses of amphetamine, a build-up of its metabolite, the false-transmitter para-hydroxy-norephedrine. This accretion of the false transmitter helped explain how amphetamine addicts were able to tolerate over time, the very large doses of amphetamine they were known to self-administer.

The Oates group's overarching interests were in drug side-effects and interactions. In keeping with the work of the group, we began accumulating demographic, prevalence and incidence data on psychotropic drug-induced side-effects, including Tardive Dyskinesia (TD) and parkinsonism (P) at CSH and in other state and VA hospitals. These institutions, with their large populations of long-term patients – many of whom had been there for years and on very high, poorly monitored dosages of antipsychotics, provided an overabundance of patients manifesting these too-long neglected side-effects.

Dr. Bass' concept for synergism at TNI began to work. I sought consultation and mentoring from several of the incumbent scientists: Jim Dingell and Fridolin were particularly helpful. In consultation with Fridolin Sulser on the pharmacology of the Basal Ganglia, we began developing a pharmacological model for drug-induced movement disorders in man: a hyperdopaminergic-hypocholinergic model for TD and the converse for parkinsonism. Jim could, amazingly, predict

for us the metabolic fate of our study compounds. The initial plans for the movement disorder studies were to use orally administered amphetamine and i.v. physostigmine in patients with TD and parkinsonism as test agents for this model. These plans were never fully implemented due to my departure from TNI. We also had basic scientists sit in on evaluation interviews with some of my bi-polar lithium patients. They were reportedly struck by the tremors and hyperactivity manifest in patients with this hyper-adrenergic disorder, observations similar to those they had made at the animal level in their amphetamine research.

The plans for the construction of the clinical ward continued apace. After much bureaucratic delay, planning, wrangling and negotiating with the State Department of Mental Health, refurbishing of the Cooper Building's third floor into a research ward-space began. The search for heavily-published, seasoned clinical investigator continued. With the advent of the Clinical Division space, John M. Davis at NIMH accepted appointment as the full-time Director of the Clinical Division of TNI. In addition, Davis was appointed Professor of Psychiatry and Pharmacology at VUMC. On completion of the ward physical facility, I discontinued my research at VUH and moved to a newly completed office on the ward at TNI. Davis recruited David S. Janowsky from NIMH to occupy the third clinical position. We quickly assembled a ward staff of research nurses and technicians and admitted a full complement of volunteer research patients, some of which were transferred from other CSH treatment units. Janowsky was a gifted ward manager and group therapist and quickly had things up and running. I shared my unpublished research data with Davis and Janowsky and put their names on my publications for an auspicious beginning of the now fully-staffed Clinical Division.

During all this, William Orr stepped down and Vanderbilt named a new Chairman of Psychiatry, psychoanalyst Marc Hollender. I was disappointed that he visited TNI only once at the beginning of his tenure. Much of his attention, however, was taken by the clamant needs and the rebuilding of other sections of the dysfunctional Psychiatry Department he inherited. Though so pre-occupied, and able to pay only scant attention to our more remote unit, he did recognize us by assigning medical students on rotation to the ward. Within a short period, however, my incompatibility with Davis became an issue for us both. The major bone-of-contention was that his vision and plans for the Division, and the daily work of the ward, gave no cognizance to the work I had done, or to any thoughts and plans I might have already developed for activities of the Division. I became increasingly excluded from the day-to-day and overall operation and planning

of the Division. I could probably have resumed my relationship with Oates' group but I was now expected to work in the long-awaited CSH clinical facility. I approached my superiors in both Psychiatry and Pharmacology for advice but received little support, except being given the precept that, in such matters, the senior person had to be supported. Hollender was clear that, though the work of TNI was of interest to him, to my chagrin, he evinced no overall interest in psycho-biology, and would not recommend me for promotion within the Department. He, furthermore, stated an intent to retain and expand the Freudian, psychoanalytic emphasis the Department had followed under Orr.

As our threesome in the Clinical Division became increasingly a Davis-Janowsky dyad, with me a superfluous monad, it became obvious that I would not be able to stay. I responded to recruitment inquiries from the Department of Psychiatry at Duke who wished to develop Clinical Psychopharmacology there. I discussed these possibilities with Dr. Bass. He cautioned that, while Psychiatry at Duke was strong and would be supportive, Pharmacology at Duke had been all but eliminated by physiologist Daniel Tosteson's subsuming it into his Department. He counselled that I would have difficulty developing clinical pharmacology without strong support from a Pharmacology department and that I should early on negotiate with Tosteson in these matters. After further negotiations with Duke, including an explicit promise from Tosteson for reinstatement of Pharmacology, and that I would be given a joint appointment in the Department, I accepted Duke's attractive offer – a full salary, a fully-staffed ward and research technician positions. I was admittedly angry and hurt by the events at Vanderbilt, but I resigned from VU and moved to Durham, NC, in July, 1971.

Davis and Janowsky remained at TNI for two more years. With their departure, the internationally renowned psychopharmacologist, Thomas Ban, assumed Directorship of the Clinical Division. Central State Hospital was later closed and demolished, ending, except for salary support, the State's commitment to TNI. Sulser moved his operation to the main Medical Center campus and continued his work there, but the TNI, as it was initially established, was effectively disbanded.

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