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Arnold, can we begin with how you came into the field? Well, let's go back to where you were born and brought up.

I was born in Chicago. My mother was a Chicago Conservatory pianist and piano teacher and my father was saxophone and clarinet playing jazz musician and band leader. My mother taught me and pushed me to study classical music. My father used records and stories to interest me in jazz. He had hung around in the Chicago jazz crowd with pioneer, Earl Hines, "the father," and his crowd, which sometimes included Ellington, and had written a piano book with him. So, my childhood was dominated by a tug-of-war between classical music and jazz. As an adult, a similar struggle dominated my work; between psychoanalysis and brain biology.

As I was growing up, practicing three to four hours a day, it was seen as virtuous to work at Bach's Two and Three Part Inventions, and "dirty" to improvise around "I Got Rhythm". I remember writing an arrangement entitled "How High the Moonlight Sonata", which my mother hated. In my early teens and then on, I settled on a piano style that was most like that of Oscar Peterson and tried, but failed, to be Charlie Parker on the saxophone. I, however, did win several American Federation of Musicians contests on classical music for the alto sax.

I have always heard patient's stream of associations like jazz improvisation, with the person's character revealed in the style of their flow of talk. Schizophrenic discontinuity and thought disorder "swing" like Thelonious Monk. Then, there was the plaintive obsessive ruminations of Bill Evans; the manic flight of Art Tatum; the psychopathy of Bud Powell. In 1997, I gave an invited address at the Fourth Experimental Chaos Conference, in which Karen Selz and I used dynamical systems' ergodic theory to quantitatively differentiate between nonlinear measures of a variety of modern jazz styles, as well as early versus late Beethoven. The styles were clearly and quantitatively discriminable.

I got interested more directly in the brain in my early teens when my dad gave me a book from the early 1900s by Roger Blatchford, called *Not Guilty*. It concerned the social psychology of criminality. It developed the position that most people weren't voluntarily evil, but, rather, their style of behaviour was the result of the interaction of the genetics of their brain and the influence of their environment during growth and development. About the same time, he also gave me an early 1930s book on physiological psychology of the brain. It was a very primitive book that discussed among other things, the shapes and bumps in the head in relationship to a person's immutable behavioural patterns.

A point of view that's old, but lost now, isn't it, the notion of the influence of physical constitution?

Well, on one hand it's lost and on the other hand, the same set of assumptions underlies much of our current theories of genetic inevitability; somatotype has been transformed into nucleotide sequences and proteomic expression with the same "anatomy as destiny" kind of finality. When I went to Stanford, having been a brain groupie during my teens, I was really disappointed to find that there were no laboratories of neuroscience or neuropharmacology.

Nothing. You actually went to Stanford in 1958?

No, I was seventeen and entered Stanford in 1951. I majored in psychology and chemistry, and spent my extra-curricular time running rats for professors in Stanford's psychology department, especially for D.H. Lawrence, and working on the unfolding of neural crest tissue to become autonomic ganglia in the embryology laboratory of Graham Dushane. He was very scholarly and quite influential in my life, somehow teaching me the transcendent feeling of the doing of research. He was editor of *Science* for several years.

I was encouraged to frame the rat data so I was getting in the language of mathematical learning theory of the sort being talked about by Sid Siegel, the nonparametric statistical whiz, and Richard Atkinson, later Chancellor of UCSD in La Jolla, and then all campuses at University of California. I was remarkably lucky to have close relationships with these men and other senior post-docs and junior faculty in psychology at Stanford.

I got to be present and participate in discussions late into the night in front of blackboards borrowing chemical kinetic equations to represent learning functions, comparing the drive reduction theories of Hull and Spence with the operant theories of B.F. Skinner and his followers. I also continued to maintain my interest in the anatomy and physiology of the brain for which I was frequently teased by these radical behaviourists.

I also had a memorable semester in a private tutorial with Albert Bandura, reading Otto Fenichel's *The Psychoanalytic Theory of Neurosis*. In my third and final year at Stanford, John Eccles's *The Neurophysiological Basis of Mind* came out, which made learning functions neuroanatomical and observable even in the spinal cord. I carried the books of Eccles and Fenichel around for years. Maybe it should be noted, relative to my later life, I also fell in love with and took courses in organic chemical reaction mechanisms. I guess I was trying to find some kind of harmony in the aggregate of mathematical, psychoanalytic, neuroscientific and organic chemical thinking. This search for accord became the signature of my inner life, but was already in place in primitive form at Stanford in 1951 and 52. It was also the framework for a lifelong conflict that remains unresolved.

Conflict?

Well, let me begin by saying that I spent close to ten years as a patient, called "candidate," in four times per week psychoanalysis. My first psychoanalyst, when I was at Tulane Medical School in New Orleans, was the New Orleans Institute training psychoanalyst, Irwin Marcus. Later, during my residency at the Neuropsychiatric

Institute at UCLA, I entered training psychoanalysis in the Southern California Psychoanalytic Institute, and spent five years with Judd Marmor.

During my first psychoanalysis, in New Orleans, I worked nights and weekends doing spinal cord research in cats under oil in the Physiology Department directed by Matt Bach, an early student of Horace Magoun, of reticular formation fame. The work itself was inspired in part by John Eccles and in part by Horace Magoun, especially the 1951 symposium, *Brain Mechanisms and Consciousness*, edited by Jasper.

I also spent a couple of years around Robert Heath and his group watching him use depth electrodes in the human septal region for stimulation in schizophrenics. He focused on the inability of chronic schizophrenic to experience pleasure: anhedonia. Septal stimulation was found to be pleasurable to these patients. They were outfitted with stimulus boxes on their belts so they could dose themselves as needed. Heath's group also was extracting plasma from schizophrenics looking for what he believed to be a unique protein fraction, something he called taraxein.

Heath was the reason I had gone to Tulane in the first place. He had promised me a place in his laboratory. He looked like Gary Cooper, and his charisma and easy familiarity with both brain biology and psychoanalysis were really seductive. His background participating in the Columbia-Graystone Project, involving selective cortical and limbic ablations in chronic schizophrenic patients as well as his psychoanalytic training under Sandor Rado made him a living representative of my fondest dreams for myself. Nonetheless, I found his laboratories too intimidating once I got there, so after a year or so, I switched to the uptown physiology department, under the supervision of L.M.N. Bach.

I published my first scientific paper in 1956, comparing brain stem descending and local spinal cord inhibition and their interaction in the lumbar spinal cord in the anesthetized cat. My second paper, delivered at the Fall Meeting of the American Physiological Society of that year, reported a relationship between medial bulbar sites eliciting descending motor inhibition under anesthesia and the same site in the awake cat generating fear behaviour, and lateral bulbar sites eliciting motor facilitation under anesthesia and out of anesthesia, pleasure, indicated by languorous purring.

In those days there was a great deal of tension between "biological psychiatry" and "dynamic or psychoanalytic psychiatry". My fellow psychoanalytic candidates and some of the teaching analysts told me directly that I couldn't be a real psychoanalyst and a biological brain researcher at the same time; that I had to choose. It would be considered silliness now but it was an issue full of rancor in those days. Biological Psychiatry was considered a "resistance" to psychoanalytic insight by many. The issue came to crisis during my psychiatric residency at UCLA's Neuropsychiatric Institute.

What happened?

I was in the same conflictual position again. On one hand, I was getting analyzed four times per week with Judd Marmor, and spending four hours a week in Southern

California Psychoanalytic Institute seminars. On the other hand, the Brain Research Institute space committee gave me the laboratory that had belonged to the psychopharmacology pioneers, Eva and Keith Killam, who had transferred from UCLA to UC, Davis.

From seed money and some NIH and State Mental Health Funds, I developed a biochemistry laboratory that studied the interactions of human limbic stimulation with corticoid release and plasma levels. We collected several times per week and several times per day, urinary corticoids and tryptophan metabolites in bipolar patients, and, studied the effects of elevated plasma and urine corticoids on tryptophan metabolism in man. Following some early animal work on hepatic enzyme induction with corticoids by Knox and his group at Harvard, my team, particularly Irene Mersol Sabbot and Robert Rubin and the clinical staff of my Neuropsychiatric Institute in-patient unit, collected urine every six hours for weeks in urinary time series in starving patients and in patients with disordered affect.

We published several papers reporting our story, principally about the metabolic evidence of the induction of hepatic tryptophan pyrolase activity in depression associated with elevated urinary corticoid excretion, and the cleavage of the indole ring leading to marked reduction in peripheral serotonin metabolites, one of which I reported in man for the first time. I got the Society for Biological Psychiatry's A.E. Bennett Prize for this work. This finding was indirect evidence of a possible brain serotonin deficiency in affective disorder. Ed Sachar, at Einstein, and Biff Bunney, at NIMH, were also following steroids in affective disorder found a peak in depression.

My fellow analytic candidates in Southern California at the time called me "the urine boiler". They teased me about trying to understand the human soul through the kidney. I just didn't want any more of what was sounding more and more like a fundamentalist religion. I finished my training analysis with Marmor, who was supportive of my biological research life, treated two training clinic patients classically analytically under supervision - three were required for institute membership - and attended analytic seminars for five years. One day I decided I had had enough.

When I resigned from the Institute, several of my candidate and analyst friends told me that no one would believe that I had resigned. They insisted that everybody would assume that I had been thrown out. That fixed it for sure. I was finished. Beyond what I had done, it seemed a waste of time. It got less and less relevant to my clinical interests, and I was finding the brain relevant research increasingly exciting. I wanted to chase the serotonin story into the brain. In addition, around that time, I had several critical clinical incidents that led me into psychopharmacology.

What were the incidents?

I guess the issue can be captured in two stories. The first story was during my residency when I was doing several months of daily psychotherapy with an in-patient. She suffered from what was known in those days as "involutional depression", which rode on an obsessive-compulsive, passive-aggressive character. She was getting worse and

worse every day. Although the supervisor recommended shock treatment, I was in analysis and in psychoanalytic seminars and wanted to see what I could do with insight. They agreed to let me keep her in the NPI hospital for months to try. The patient was the unmarried older sister of a bookkeeper. She was the caretaker of her aging mother, and in her early fifties she began to lose sleep and weight, experienced a marked increase in her obsessive-compulsive traits and became suicidal.

My psychotherapy was about her unconscious frustration and rage; her resentment of her sister, and mother, for stealing her life from her. This treatment appeared to be making things more painful for her. She, of course, felt accused, but denied it all and the talk only made things much worse. All the while she continued her passive aggressive praise of me for making her so much better. I was growing desperate because I didn't want to use ECT, but saw it as inevitable.

It was at this time, in 1960 that I got a drug from a detail man, a new Ciba-Geigy drug, imipramine-Tofranil. It was initially thought to be antipsychotic, but was showing antidepressant actions. I will never forget the third day of her treatment with imipramine. I was late for the daily visit, and when I entered her room, she looked at me with obvious irritation, for the first time, and said, "You're late". She had never been able to speak to me, or I think almost to anyone, like that. In the next three weeks, her syndrome of over two year's duration disappeared! Her sleep and appetite returned; her delusions of "smelling bad" and "contaminating the chairs if I sit down" were gone. She was easily able to speak about her "boxed in" state and began to make new life plans for herself.

From a dynamical point of view, imipramine reduced her separation anxiety - Don Klein developed this thinking most clearly - which trapped and unconsciously enraged her; her felt anger made her feel like a "bad person". She described how happy she was with her new "freedom to choose". That was my neuropsychopharmacological moment! I saw that not only symptoms but permanent characterological features of a person could be changed with these new psychopharmacological agents. Who a person was could be altered; not tranquilized, not muted, not speeded, but changed in fundamental ways such that the "new person" was not capable of manifesting the presenting illness.

It was about this time that I began a long lasting and close relationship with Nathan Kline, known for his pioneer work with reserpine and monoamine oxidase inhibitors. Nate's real greatness was in the intimate observations he made on the patients he was treating with drugs. When we talked, it was inevitably about how the drug influenced subtle aspects of the whole person, his fantasy life, his sexuality, ambition, aesthetic tastes and appetites, and subtle aspects of the therapist-patient interaction.

Our relationship lasted until his death in the late 1970's. Nate was known as a wild, drug wielding, cowboy. What most people didn't know about Nate was his subtle, highly personal, psychodynamic view of psychotropic drug actions. He saw his drug treatment patients over significant amounts of time using long term follow-ups.

People came from all over the Country to see him. He was a marked influence on how I practiced psychiatry. When I would notice a drug induced change in a person, even not relevant to his presenting disorder, say lithium reducing the obsessive urges to gamble or binge drink, I would call and talk to him about it. We spoke about lithium “slowing down” internal processes sufficiently to allow good judgement to play a role in its effect. I always took him seriously, even literally, and he was usually right. For instance, I studied lithium effects on brain enzyme kinetics, and made some computations concerning measures of diffusion in lithium-structured water; all of it pointed to a “slowing” as a global phenomenon.

For the rest of my professional life, I thought of effective psychopharmacological treatment as changing a person into someone else who was less vulnerable or even incapable of having the psychiatric disorder with which they had originally presented. I saw, and see, drugs as altering the defense pattern and strength of the person, and that this, secondarily, becomes therapeutic with respect to the patient’s diagnosis. There must be a psychobiology of character and its changes.

During my stay at UCLA in the early and middle 1960’s every patient got an MMPI and therefore a characterological profile. I watched drug treatment change the “shape” of the MMPI profile, particularly in the Axis II characterological scales. Tricyclics reduced or eliminated the MMPI profile of a ruminator. Low doses of antipsychotic changed the Sc-Pd MMPI profile, called, but not really, “schizoid-psychopathic” character. Anti-epileptics changed the threshold of the hysteroid-impulsive ego disruption of the Hy and Hs (hypochondriasis) parameters. Acute changes in anxiety, Pt (psychasthenia) and D (anxiety, depression) were to be expected, but changes in indices of long term character patterns were not. Many wonderful studies by others have since supported this kind of thinking since those early, “pre-scientific” days. Like Chinese medicine, rather than emphasizing DSM-III Axis One catalogued primary symptoms, I was always most aware of the Axes Two dimension, the patient’s character and personality and let these variables play a significant role in drug choice and dose.

This theme found its way into my neurobiological research, as well. Our laboratories focused on long lasting psychotropic drug induced changes in long lived macromolecular reflections, such as the neurotransmitters’ rate limiting biosynthetic enzymes and the sensitivity state of the relevant receptors, as representative of characterological states. These were the changes invoked by chronic administration of antidepressants and antipsychotics in experimental animals, and I viewed these changes as the neurobiological correlates of characterological change.

The second story is more about the state of psychiatry in the early 1960s. I went to my first American Psychiatric Association meeting and also to the meetings of the Society of Biological Psychiatry and of the American Psychoanalytic Association. Once, at a luncheon with the biological psychiatrists, I just happened to be sitting across the table from a very thin, bearded, threatening looking man in his late fifties who described his current research project as doing “ice pick lobotomies” on “acting out adolescents”. This

was, as I later learned, my first contact with Walter Freeman, the major protégé of the Portuguese Nobelist, Antonion Moniz, who invented the lobotomy.

Terrified, I ran across to the Waldorf Hotel where I thought the psychoanalysts were meeting. Breathless, I entered a big meeting hall and found a seat in the corner. Lo and behold, the man in front was speaking Yiddish. Since I knew that there was a heavy Jewish membership in the psychoanalytic societies, I wasn't surprised, at least for a little while. I was sitting there, uncomprehending, for about twenty minutes before I saw a sign in the corner that said B'nai B'rith. It was a meeting of the Jewish advocacy group, not the American Psychoanalytic Association! So that was what a brain groupie was faced with in the late 1950's and early '60s. A choice between lobotomies or a Jewish fellowship!

Were you teaching then?

Yes, as a NIMH Career Teacher Awardee in 1962, I developed the first undergraduate medical school course in clinical psychopharmacology at UCLA. It was a three-week course, taught within the psychiatry block in the third year. For drug indications, their mechanisms and their effects I combined two points of view: neurobiological mechanisms of action that included biogenic amine dynamics, limbic system function etc. the basis for which was taught by Wallace Winters and Charles Spooner in the Pharmacology Department, and a psychoanalytic view of personality and character. Much of the clinical material was from my own Beverly Hills-Brentwood practice, which I maintained for about 40 hours a week with a full Saturday, done after 4:00 PM each day.

It was the early 1960's and I was doing dynamically oriented psychotherapy along with psychopharmacology. I saw each patient one, two, or more full "fifty-minute" hours a week with or without drugs. The current practice, the very short time spent by psychiatrists with patients, using powerful drugs that make major global changes in personality, most of which they are unaware, is upsetting to me. These powerful drugs influence so much of a person's inside and outside reality, and so little of what is being changed is being observed by the psychiatrist. I see it as insurance plan supported very bad practice.

What do you mean by psychopharmacology from a personality dynamics point of view? I actually talked about it for years and wrote about it for Judd Marmor's recently republished book, called *Modern Psychoanalysis*. I called it "dynamic psychopharmacology". I was talking a lot at that time with Donald Klein, of similar bent, who was studying the relationship between personality type and drug responses. For example, Donald Klein described two different drug responsive anxiety syndromes.

Many others were also working in this area. For example, DiMascio and Gerry Klerman described the poorer response of hyper masculine types to non-motor activity promoting phenothiazines, such as Thorazine, compared with Stelazine (trifluoperazine). Of course, the new antipsychotics, with considerably less extrapyramidal influence mitigate this difference. A "fat and sleepy" depressed person responded better to monoamine

oxidase inhibitors, and the “thin sleepless” depressed person was more responsive to the tricyclic agents, such as Tofranil.

I insisted on once, twice or more a week of close clinical, full hour attention to patients on psychopharmacological agents, from my senior residents. This yielded regular discussions of the subtle and global personality properties of the drug response. Mortimer Ostow continued psychoanalysis with patients taking psychotherapeutic agents and spoke of descriptors such as the amount of “extrapyramidal libido”. He spoke of titrating psychic energy using blink rate.

I was convinced that the tricyclics reduced inertia and facilitated action in depressed patients, so I extended the observation. In 1962, I published several papers with evidence that Parkinsonian rigidity and inertia, not tremor, was almost completely mitigated by tricyclic antidepressants. I called it “Motivation and Ability to Move”. The neurosurgeon, Robert Rand, at UCLA said that previously poor prognosis Parkinson patients on tricyclics became good candidates for surgery, having lost their rigidity which was not subject to improvement by pallidectomy. About the same time, I also worked with Rand and Robert Rubin, my students, to show that stimulation of the amygdala in their electrode implanted temporal lobe epileptics increased plasma and urinary corticoids, while hippocampal stimulation reduced plasma and urine levels. In my course for medical students I was speaking of amygdala fear and rage and hippocampal peaceful transcendence.

I commuted to Boston once a year or so to attend Normand Geschwind’s clinic and shared dinner with Harvard’s neurology professor - who should have shared Sperry’s Nobel Prize for his theories of hemispheric “disconnexion” syndrome - and spoke with him about his remarkable collection of temporal lobe syndromes. His transcendent, asexual right lobe syndromes reminded me of St. Paul and some of the phenomena I experienced during the effects of LSD, which I obtained for personal experimentation from Barbara Brown at the Los Angeles VA Hospital. I was immersed in Barbara Meyerhoff’s studies of the Hiuchol Indians who took Peyote with their ritual practices. I was also one of Sacha Shulgin’s human subjects when he was developing the methoxy- and halogenated-amphetamine series, one of which is Ecstasy.

There were seven of us, Sacha Shulgin volunteers, with identities known only to Sacha. We each sent him our notes on our subjective observations after taking the various compounds and doses that he sent to us. I was also involved in some of the Army Chemical Corps conferences on the subject of hallucinogens. I put the phenomenology of all of this together in a 100 page essay developing a “drive-arrest-release” neurobiological theory of transcendence. It was called *God in the Brain*. It was published in *Psychobiology of Consciousness*, edited by Davidson in the mid 1980s. I still get reprint requests for it. James Austin’s book, *Zen and the Brain* used this theory, and some of the experiences were the substrate for my Simon and Shuster Book about phase transitions in man called *Coming of (Middle) Age*.

You said at the beginning of this interview that you began to chase the serotonin story.

While moving from UCLA to UCI in 1965-6, and then after being appointed in 1968-9 Founding Chairman of the Department of Psychiatry at UCSD, in La Jolla, I put together a team to study the neurochemical and animal behavioral correlates not of the initial responses to psychotropic drugs, such as blocking uptake, releasing monoamines, receptor agonistic action, etc., but rather the longer term, what I called adaptive, changes when the animal, rats, was given drugs regularly over days and weeks. Regimes of the sort used in real clinical situations. That “latency to action” was the theme of almost twenty years of work, before I changed my focus to dynamical systems in neuropsychobiology, and my following 18 years of work with Karen Selz and others in the Mathematics Department at FAU, in Boca Raton.

The group at one time or another at UCLA, UCI and UCSD included Drs. Lee Poth, Wallace Winters, Charlie Spooner, David Segal, Mark Geyer, Ron Kuzenski, Suzanne Knapp, Pat Russo, Louise Hsu, Wilson Bullard, and later, Martin Paulus, Steven Gass, Peter Leopold, and others.

Lee Poth was particularly important in organizing and moving my laboratories from UCLA to UCI, and then again to UCSD. I don't think I could have done it without her. She was not only the one that best articulated what we did in my laboratory. She also was the one who found the tryptamine methylating enzyme in rat and human brain, a fun thing to think about with respect to the brain making its own hallucinogen, DMT. Richard Wyatt explored this possibility extensively. Lee later went on to work with the Nobelist, Julius Axelrod who also, among his many accomplishments, was a very significant contributor to the biogenic amine methylation story.

The twenty plus years of research work, from 1966 to 1982 that followed was about “adaptive regulation”. It was our theory that the brain's molecular biological and biochemical adaptation to the perturbation by a drug, not its initial action, was the mechanism of its therapeutic efficacy. Tricyclics acute blocking of uptake in biogenic amine synapses was followed by a long lasting adaptive decrease in the rate limiting enzymes, tryptophan hydroxylase and tyrosine hydroxylase, for the synthesis of serotonin, norepinephrine and dopamine, as well as reduced sensitivity of their receptors. I saw the drug induced, long lasting changes in the biosynthetic and receptor proteins as representative of the chemical “characterological” changes required to successfully defeat the pathophysiology. It was, once again, a way of fitting psychodynamically and neurochemical thinking together.

This kind of talk sounds a lot like Peter Kramer's, *Listening to Prozac*.

Exactly. I think we still haven't psychoanalytically or neurochemically untangled the neurobiological or dynamical-characterological relationship between the loss of sexual libido and the improvement in disposition that often occurs together in people given SSRI's. Norman Geschwind spoke of the right temporal lobe epileptic change in personality toward a beatific kindness toward everyone and loss of interest in sex.

You had a pretty talented group of co-workers.

I have been very fortunate that way. I was always looking for researchers who would do what they were doing even if they didn't get paid for it. They made a remarkable series of findings. David Segal was the first to show that intraventricular norepinephrine in rats produced behavioral activation. He also developed an animal model for adaptive regulation, and perhaps bipolar disease, using the chronic drug administration paradigm. He showed that daily administration of reserpine produced gradual decreases in spontaneous motor activity to almost immobility, until day nine at which time that rats within a few hours became suddenly, continuously hyperactive, night and day, for several days. The change happened suddenly, and we wondered whether this was a model of what Biff Bunney called "the switch" into mania from depression in bipolar disease. This work was published in *Science*.

Another yield of the long-term drug strategy was David's discovery that intermittent administration of amphetamine induced progressive increases in sensitivity, instead of the expected tolerance, to the drug. The supersensitivity lasted months in rats. Several of our abstinent ex-addicts working in the drug treatment program I started, the first methadone maintenance program in San Diego, tested which flavor would be best. It was remarkable that they were drunk for hours from a highly diluted single teaspoon full of methadone that I didn't even feel.

In the early 1970s in my laboratory David Segal was the first to discover behavioral sensitization to a psychopharmacological agent, and Ron Kuczenski to demonstrate allosteric regulation by a brain enzyme protein. He showed that heparin, chondroitin sulphate and other membrane components activated tyrosine hydroxylase, the rate-limiting enzyme for norepinephrine and dopamine. Among the many other things, Suzanne Knapp discovered that lithium stimulated, and cocaine blocked, the tryptophan uptake path in serotonin nerve endings. Chronic lithium created a serotonergic buffer: increasing serotonin synthesis by increasing tryptophan uptake against a compensatory decrease in the rate-limiting enzyme, tryptophan hydroxylase, reducing serotonin synthesis. The range of variation of brain serotonin was thus constrained below and above into a narrow range. Mogens Schou, who followed John Cade in pioneering lithium use in affective disorders, told me that he liked our serotonin buffer theory, and I was told that he used it in several of his lectures. The principle of this kind of buffer has recently been applied to other synaptic chemicals such as the excitatory glutamate neurotransmitter. I was given the Foundation Prize in psychiatric research by the APA for this work in adaptive regulation and its manifestations in the multi-phasic actions of lithium.

Somewhere in this time, we also developed what we called "the NIMH neuron". Several nonlinear mechanisms were working to modulate the function of biogenic amine synapses at the same time, and we studied them in parallel. For example, with respect to the serotonin neuron, we studied simultaneously tryptophan uptake, tetrahydrobiopterin cofactor generation, allosteric state of the rate limiting enzyme, tryptophan hydroxylase activity, vesicular storage and release mechanisms, cellular synthesis of tryptophan hydroxylase, variable rates of axoplasmic flow of the enzyme,

nerve ending release and reuptake of serotonin, presynaptic feedback via autoreceptors, and dependence of postsynaptic action upon the variable sensitivity of multiple serotonin receptors. We studied all of these mechanisms simultaneously, in addition to behavior in response to psychotropic drugs in rats.

What was the relationship between these basic studies and clinical psychopharmacology?

Much of the creative inspiration about psychopharmacology in my teaching to medical students and residents, as well as in my clinical practice came from my annual two week meetings with The Denghausen Group on one or another Caribbean Island. It was like a meeting of gris-gris men of brain drugs.

What was the Denghausen Group?

Beginning in the middle to late 1960's, organized by Nathan Kline and supported by the Denghausen Foundation, an international group of pioneering psychopharmacologists met every 2 years for 10 days to 2 weeks to discuss subtle clinical psychopharmacology issues. We each gave informal talks involving our clinical observations or new, usually unpublished, basic research findings. We had, sometimes heated, discussions in the mornings and then had the, afternoons free to enjoy with our significant others. It was a diverse collection of scientists, including two Nobelists. The Denghausen Group included Nathan Kline, known for his work on reserpine, monoamine oxidase inhibitors, lithium for alcoholism; Heinz Lehman, a Canadian pioneer who in his long term collaboration with fellow Canadian, Thomas Ban, both significant pioneers in psychopharmacology, introduced and elucidated the use of phenothiazine antipsychotic treatment in schizophrenia; Floyd Bloom, a world class neuroanatomist studying the physiology of brain stem amine neurons, actions of peptides; Larry Stein, known for self administration and self stimulation in the application of Skinnerian learning models to psychopharmacology; William (Biff) Bunney, a classical pioneer in neurochemical and hormonal studies of affective disorder, head of the clinical research unit at NIMH; Arvid Carlsson, Nobelist discoverer of role of dopamine, its relationship to the actions of antipsychotics and its metabolism among many other things; Philip Berger, an outstanding Stanford psychopharmacologist; Jose Delgado, a Spanish neurosurgeon famous for arresting a bull at a distance with caudate stimulation and of course, fundamental human neurophysiological discoveries; Roger Guillemin, a Nobel Prize winner for his discovery and sequencing of several important neuropeptides; Mogens Schou, responsible for the clinical development of the use of lithium in affect disorder; Jules Angst, an important European psychopharmacologist responsible for many large population psychiatric drug studies; Ed Sachar, an early and important discoverer of the corticosteroid responses in depression and its recovery suggesting that depression "is a hypothalamic disease", and who, in his characteristic humble way, gave me credit for that phrase, but it was his; Julian Mendlewicz, a creative and productive academic Belgian psychiatrist and psychopharmacologist; Alec Coppen an important English psychopharmacologist, who was known for his careful long term drug studies in psychiatric disorders, and me.

I learned very valuable, empirically useful clinical things from the Denghausen group, like the use of low dose lithium to potentiate uptake inhibitors, or carefully potentiating the action of monoamine oxidase inhibitors with tricyclics, though the warnings said not to. I learned about potentiating both antidepressants and antipsychotics with small amounts of thyroid hormone in euthyroid psychiatric patients, and the use of lithium to reduce impulsive acts, such as suicide or binge drinking or gambling. The addition of tryptophan to a monoamine oxidase inhibitor regime potentiates their antidepressant effects. S-adenosylmethionine can be useful as a health food, over the counter antidepressant. I learned these and so many more things.

Every two years we went to another Caribbean Island. When we went to Haiti, Nate arranged for us to spend a few days with voodoo priests, who had various potions that served as the vehicle for the transformation of a person into the walking dead, a zombie. We took a little and found that it slowed the heart and respiration, as well as temperature and metabolic rate, so someone could be buried alive for several hours and then return. We also learned how the zombie ceased to exist to the society. They walked by him as though he weren't there. Nate took some of the potion to his labs, now the Nathan Kline Institute, for analysis. We never heard more about it. Nathan wouldn't talk. Incidentally, I appointed Nate Kline a part time Clinical Professor in my Department of Psychiatry at UCSD in La Jolla. I was happy that he claimed this affiliation in his books.

As I understand it, when you started the Department of Psychiatry at UCSD in 1968 you had a relatively free hand in recruiting and were given many FTEs. Is that true?

It's hard to believe, but in addition to several clinical billets at UCSD's VA Hospital and more at its County University Hospital, I got 12 tenure track academic positions. And once again, I was faced by the state of psychiatry at that time, a split between a dynamic, interpersonal orientation and a behavioral neurobiological position. How I solved this problem may have more general importance.

My first hire was Sam Barondes, who was a well-trained psychiatrist as well as an accomplished molecular biologist out of the laboratory of Nierenberg, the Nobel Prize winner. For 1969, that was a strange combination as well as a unique appointment in a department of psychiatry. He worked on problems ranging from RNA in memory transfer, membrane-involved glycoproteins in cellular organizations like the transition of the slime mold to a fruiting body when food gets short, and, other fundamental biological problems. He wound up Chairman of the Department of Psychiatry at the University of California in San Francisco.

My second hire, Lew Judd, was a very promising child psychiatrist and clinical researcher. His career path in our department led to his being head of the National Institutes of Mental Health for a time, before taking over my chairmanship at USCD. Almost every kind of psychiatry was represented in our department. Psychoanalytic clinicians were intimately involved in training our residents, as were the brain chemists and molecular biologists.

In addition, we developed a deep area of neuropsychology with the likes of memory theorist, Larry Squire, who was later President of the Neuroscience Society. The residents were also exposed, and often participated in, basic pharmacological studies going on in the department. Even in psychotropic drug treatment, we emphasized the necessity of psychiatrists to have an intimate knowledge of the patient's inner life, whether they used drugs or not. The department also believed in community service.

We established the first methadone maintenance program in California in a network of over 12 clinics with paraprofessional therapists. I went to the University of Chicago for a month and studied with Jerry Jaffe and Danny Freedman, who had the only methadone maintenance clinic after the first one of Vincent Dole's at Rockefeller University. We also established a very sophisticated abortion program involving extensive counselling before and after the procedure. Recall, San Diego was second to only Orange County in Republican Fundamentalism so you can imagine that it made a lot of noise in the newspapers. Between our research and clinical programs our department was receiving several million dollars a year from extramural sources.

From psychoanalysis and molecular biology to methadone maintenance. For its day, it was kind of a wild department.

Even a little bit of potential ACNP gossip comes up in the recruitment context. A Chief of Psychology position opened at the UCSD VAH, and I coupled that with a tenure track appointment in the University and tried very hard to recruit Oakley Ray, with the hidden agenda of moving him and the ACNP headquarters to La Jolla from Vanderbilt. I couldn't get his appointment past the politics of our Department of Psychology, which was anti-clinical and mathematically-experimentally oriented. Several late night committee meetings were to no avail.

That was a loss for us, not just politically, of course. Oakley believed in personality and character as the underpinnings of an understanding of psychiatric disorders and psychotropic drug treatment. He annually used my study of "personality and position in the NFL," published in my book *Nightmare Season*, printed by Random House in 1976, in his classes at Vanderbilt as a way of introducing personality theories.

Before you leave this topic, let me ask you more about the lady, who was actually depressed, who was bonded to Tofranil. Would you describe her change of personality, which is a little bit like the kinds of things Peter Kramer was describing in *Listening to Prozac*, a very different understanding of what's going on, compared with what has since become the dominant understanding?

Yes, and having tried to equate long term macromolecular changes in response to psychotropic drugs as the underpinnings of drug induced personality changes, it then was a challenge to see if we could develop a research strategy that would reflect objective measures of the change in "style" of the stable state besides the less meaningful change in the mean values of measures. As luck would have it, in the 1960s and early 1970s, applied mathematics and statistical physics was going through a significant revolution with respect to their approach to determinism and randomness in

physical systems. I saw that this would give us a way of objectively studying changes in stable neurobiological states.

It was a system of thought and measures across basic clinical neurobiologically relevant variables. I first made contact with this way of thinking in the work of Steve Smale and Mo Hirsch at Berkeley, and Feigenbaum in Los Alamos and, of course, in the work of my good friend Benoit Mandelbrot, then at IBM. I also became close friends with Mike Shlesinger, a world-class statistical physicist. They, generously, spoke with me, tutored me, gave me papers and boy did I study! I studied hours and hours every day and long into the night.

Dynamical systems involved nonlinear differential equations, differential topology, matrix and group theory, nonequilibrium thermodynamics and statistical physics. All this stuff underlies what is now called "chaos and fractals". How to characterize the behavior of whole systems composed of many coupled parts, such as brain and behavior and its psychopharmacology, were natural contexts for the study of complex systems.

I organized the first conference about this relevant to psychiatry "in the world", at the annual meeting of the ACNP in 1982! It involved Mark Geyer, Cindy Ehlers, Suzanne Knapp, Pat Russo, and others. I tried to explain this area of research to the psychopharmacology community in the *Annual Review of Pharmacology and Toxicology* in 1984. Then I got the NIMH to sponsor an international conference with the mathematical, physical and biological leaders in the field held at the auditorium in the intramural program at NIMH. There were about three hundred attendees. They ranged from mathematicians to clinical psychiatrists with many physicists. It was published as Volume 504 of the *Annals of the New York Academy of Science* in 1987.

It was about this time that it was clear I was committing the rest of my life to chasing this fusion of nonlinear dynamics and statistical mechanics as applied to neurobiology. It was at this time that I had the great good fortune to be joined by Karen Selz who was both brilliant and computationally gifted. She saw the blend of qualitative dynamics and quantifiable statistics immediately and we've been working together since. Early in this era of applied dynamical systems, Karen did foundational work elucidating universal classes of dynamical systems styles which mapped onto patterns in human computer mouse behaviour, both of which she related to personality. Then as an encore, she exploited the Thurston-Milnor theorems, showing one could generate any sequence by changing the parameter of the one dimensional tent map, to show that dynamical signs of contrasting personalities could be represented by a single value of a single parameter.

Then, a burst of papers followed, that hasn't stopped. We wrote a personality pattern long paper in *Psychiatry* in 1995. For the most part, however, we have published in physics and biophysical journals as our efforts at intrusion into mainstream psychiatry and psychopharmacology weren't getting anywhere.

The nonlinear dynamics, dynamical systems point of view turns out to be a very powerful way to look at psychiatry and psychopharmacology. For example, in complex systems, there are a relatively few “scenarios”, or syndromes. It is paradoxical that the higher the apparent dimensionality of a system, the more coupled the variables, the more likely the system would be to obey only one of a fewer, and fewer set of evolutionary narratives. The implications for brain drugs are many. For example, we all admit now, in spite of the “receptor binding pseudo- specificity” that all effective drugs are “dirty”, i.e. critically influence the involvement of many, many mechanisms that we know about, and probably many more that we don't.

In spite of the multiplicity of deterministic mechanisms, we observe a singular, or few, global states of mood and/or cognitive patterns. These patterns can be represented as graph-diagrams in what is called “phase space”, with statistical patterns of behavior observed on this phase space. This radical “theoretical reductionism”, and not physical reductionism of the “behavior to a molecule” sort, of many simultaneously active systems to behavior that can be represented in two or three dimensions and with one or two parameters, speaks to the essence of dynamical systems. Doesn't that sound like many or most of our researchable problems?

From a measures point of view, it is the pattern variability around the mean function that characterizes the few dynamical states that we can use to study basic and clinical variables relevant to a drug action. These studies turn out to be a deeper look into what had previously been called “noise” or “error”. The tools of the measure part of dynamical systems made it possible to describe “what kind of randomness” we are talking about. One might re-perceive personality as the expected pattern of variation around mean tasks. Not if, but how do you make your bed? Not if, but how do you drive your car? What sort of relationships do you have with others? And the representation can be quite abstract.

Selz has used these techniques on computer mouse trails made by unaware subjects as they carried out simple computer tasks. She was able to clearly discriminate between normal persons with obsessional character, hysterical or borderline personalities. Sometime, the patterns in observables can be diagnostic.. For example, in many systems, increasing regularity augured pathological fixation and stereotypy with loss of flexibility, thus physiological control with resulting disease of the system. Instead of the little ups and downs of normal mood over time, the system becomes coherent at many scales in the form of manic-depressive illness.

How did this kind of thinking show up in your laboratory?

Beginning in the early 1980s I was involved in the application of dynamical systems and measure theory to brain enzyme activity as influenced by psychotropic drugs. Pat Russo and Suzanne Knapp developed *in vitro* preparations that allowed the study of critical brain proteins “in motion”. The fluctuations in the rate limiting enzymes - “product concentration frequencies”-for serotonin and dopamine, tyrosine and tryptophan hydroxylases were studied as time series, and manifested classical chaos and fractal hierarchies of scale in brain enzyme activity. The patterns of fluctuations were sensitive

to psychotropic drugs. Lithium decreased the amplitude and increased the frequency of fluctuations in many systems, from tryptophan enzyme fluctuations to spontaneous neuronal firing patterns to the EEG and MEG. Also, it should be noted that it was in our laboratory that Mark Geyer began his remarkable program of work leading to startle habituation and its failure as an animal marker for antipsychotic and other psychotropic drugs. Martin Paulus translated the ergodic theory of dynamical systems into the analysis of varying partitions of time series of rat and human behavior in such a way that an entirely new set of measures were used to demonstrate drug effects, strain differences, and with David Braff, psychopathology in man. This occurred in the 1980s and early '90s.

It all sounds very exciting but honestly, I haven't seen much evidence of this point of view on the current psychopharmacological scene, either in clinical or basic research.

That's a personally painful truth. I, and my co-workers, have spent years working in dynamical systems in brain and behavior, and little by little it got corralled into biophysics. Physics, biophysics and dynamical systems meetings are those that this kind of work gets presented in. I received a MacArthur Prize Fellowship in theoretical neuroscience from 1984 to 1989, the money from which I used to spend years at European mathematics institutes known for these kinds of mathematics and physics.

Rene Thom invited me to the Institute des Hautes Etudes in Bur sur Yvette twice, for a year each time. Both times were buried in studies with their very generous and helpful mathematicians, particularly David Ruelle. From Thom, I learned differential topology; and from Ruelle, ergodic theory and statistical mechanics. I then spent almost a year at the Warwick Mathematics Institute as a guest of Christopher Zeeman who taught me bifurcation theory and then I studied with their world-class ergodic theorists: Peter Walters, David Rand, Tony Manning and Mark Pollicott.

Karen Selz, who has a joint degree in mathematics and psychology and I wrote dozens of papers using these theoretical and computational methods in cardiac dynamics, brain stem neuron time series, EEG, and human behavior, all with implications for psychopharmacology. With Knapp and Russo, I showed these kinds of dynamics in substrate to product concentration fluctuations of biogenic amine enzymes and their receptors. The first report on this was out in the first volume of the Journal of Neuroscience in 1981. Sharing one of Roger Guillemin's grants at Salk, I began to apply symbolic dynamics to analyse and predict amino acid sequences as hydrophobic moieties to see if that might "match" ligand and receptors. The scheme was not much good. It was then, that my co-worker, Selz was inspired to use a particular system of eigenfunctions, hydrophobic eigenfunctions, which demonstrated matches between ligands and their receptors. Selz and I used these techniques to successfully design dopaminergic and muscarinic peptides that modulated the sensitivity and allosteric properties of the D2 and M1 receptors. Leon Glass, the Canadian physicist, took this point of view into cardiology and brain science. Paul Rapp, an Oxford mathematician and Drexel University physiologist was a major contributor to applying it in EEG, psychotherapeutic interactions and other aspects of brain science. Jim Collins and his

group at Boston University, and Ari Goldberger, once a post doctoral student of mine, with a very large nonlinear dynamics center at Harvard, are major contributors to physiological research using dynamical systems methods. Cindy Ehlers at Scripps Research Institute has applied these techniques to the analysis of neurophysiological data. But except for an occasional inspired physicist writing in physics or biophysics journals, very little has found its way into the literature of psychopharmacology or psychiatry.

What has any of this new field amounted to as far as the research or practice of top-drawer psychopharmacology as represented by the ACNP membership?

Actually, very little. Following the dynamical systems panel I arranged at the ACNP annual meeting in 1981, I have been unable to present or publish about this field at psychopharmacology meetings or in its journals. For example, since the 1980's the ACNP program committee has rejected high quality panel submissions, composed of the best and most accessible mathematicians and physicists. I suspect if I didn't have the energy and smarts that Karen brought to our work, I was ready to quit.

Why is that?

Besides the deep suspicion and dislike of most biologists about things mathematical, I would say it was the excitement of the more concrete and obviously biologically relevant competing fields. The incredible technological sophistication and ease of modern molecular biological techniques, the emergence of microfluidics and high throughput screening methods, as well as the intuitive appeal of modern brain imaging that take psychiatry back to our turn of the 19th Century neurologizing, has all but masked this emergence of dynamical systems theory and its attendant methods.

Can you give some examples of how dynamical systems thinking might be applicable to a practicing psychopharmacologist?

I have three favorite examples, though I could give you many. Most psychopharmacologists are probably familiar with both phenomena, but don't think of them from this perspective. The first involves nonlinear dose-response curves. By that, I don't mean "S" shaped curvilinear functions, but a result of a nonlinear function, or operator $f(x)$, defined by what it is not. In a linear operator 2 times $f(x) = f(2x)$. In a nonlinear system, 2 times $f(x)$ doesn't = $f(2x)$. In such systems, in some drug dose regimes, more drug leads to less effect and/or less drug leads to more effect.

Back in the tricyclic days, before the popularity of the SSRIs, much work was done with tricyclic blood levels in relationship to clinical efficacy looking for "the therapeutic window". This is quite a general property of psychotropic drugs, which may even demonstrate iterative saturation plateaus. This implies that one might be able to treat a psychiatric disorder optimally with very low doses of drug, then again at medium doses of drug, and then again at high doses of drug. This also means that if one is not getting the desired effect, there are dynamical arguments for lowering the dose as well as for increasing it. Of course, with respect to side effects, finding the lowest effective dose would be desirable. I would also say in this context that PDR recommended doses for psychiatric drugs have less meaning than in more simple systems.

The second example is what might be called the “curse of polypharmacy”. Since the dynamics of complex nonlinear dynamical systems representationally simplify with more and more parameters, a patient with a complex psychiatric illness whose personal pharmacopoeia reads like a drug store pharmacy is not necessarily being poorly treated. A carefully followed patient with whom a physician is using drug choice and dosage range on a trial and error basis may eventuate in a treatment program that includes, for a real example, three antihypertensives, two or three antidepressants, a β -blocker, a calcium channel blocker, a bone saving biphosphonate, a personality changing antiepileptic, a stomach saving H₂ transport blocker, aspirin, a prostaglandin blocker, lactoferrin, ascription, a calcium-magnesium supplement and some herbal preparations.

Two generally true circumstances underlie the theory of thoughtful, therapeutic polypharmacy: (1) Drugs given for a single somatic locale act on biochemical mechanisms throughout the body in such a way that their nonlinear interactions can produce an unknown except empirically global physiological state of health; (2) The more independent variables, “handles” to manipulate, the greater the likelihood of finding and stabilizing even a small available parametric space of healthy function while minimizing unwanted effects. Rene Thom, Chris Zeeman and their students studying discontinuities, “bifurcations,” “catastrophes”) in real dynamical system, such as the regulation of thyroid function and immunology, proved that the more dimensions, “controls,” “handles”, one adds to a nonlinear system, the easier it is to find and stabilize a very small island of health totally surrounded by oceans of disease.

Another example is the remarkable observation we made on the saturation kinetics of brain tyrosine hydroxylase, the rate-limiting enzyme for dopamine and norepinephrine. We saw iterative saturation plateaus with bifurcations, discontinuities between sequential regimes. We saw different sizes of dose response curves suggesting that for some brain systems there are very low dose efficacy and very high dose efficacy regions. This confirms some clinical experience. I truly believe that for given patients and under propitious circumstances, one can obtain remarkably good clinical results with very low doses, far below the recommended dose. What one is looking for is the therapeutic island, not a sufficient amount. Dynamical systems give the practitioner a context for many counter-intuitive but phenomenologically observable clinical events.

Why did we lose this kind of view of things during the 1960's and 1970's? Did we lose it because we have gone down into a very phenylketonuric view of the psychiatric disorders and that's the way they've been leveled here. It's a very antibacterial view, almost. What you're actually describing is something much more subtle and nuance, which has risen its' head under various rubrics every so often over the years, but we've lost it, haven't we?

And the painful part is that the ACNP membership has, in my lifetime, moved from being a revolutionary place of respite and generation of new thinking about brain biology applied to psychiatric disorders, to what I see as a source of conservative inertia. The group feels comfortable mimicking the current basic science found legitimate by internal

medicine and other physician groups, but refuses to see itself as a potential font of another whole vision of the human body given by dynamical systems. We who study “dynamics”, we who are interested in the “whole person”, have resisted the mathematical-physical system of nonlinear global dynamical systems. One of the important mathematicians in this area, Ralph Abraham at UC Santa Cruz, says it will take a hundred years for what I think of as the real underlying scientific basis of psychiatry and psychopharmacology to be acknowledged as such.

How do you feel about that?

I have to resign myself to this opinion, as well as to the fact that I probably won't live to see it. I'm counting on Karen, among a loving few, to carry on and expand the message.

I can see where you're heading been but even me, an English-educated fellow, has had no training at all in this way of thinking. It will need to be reinvented. We've now got managed care. You've got to treat in 15 minutes. How can we ever reconcile that?

I don't know. Right now, I think the very best treatment would be if a general practitioner would give the drugs and manages the side effects, and a psychologist would listen to the patient who gives an account of the changes, if any, good and bad.

The full range of change, right?

Right. Thank you for putting up with me.