A CAREER IN BIOLOGICAL PSYCHIATRY

HERBERT MELTZER

Why did you go into medicine

Why did I go into medicine? I came from a family of very bright people but who didn't have the opportunity for higher education. The first really educated person who came into my life was the general practitioner, who treated my family. He was someone I esteemed greatly. I had a couple of serious illnesses when I was a kid. Once I got rather extensive second degree burns, which he helped me survive. I was thought to have a heart murmur, which probably was not the case. Nevertheless, it led to a certain amount of contact with doctors and a genuine respect for the profession. As I grew older and took science courses in high school, I started to think of myself as potentially going into medicine. I registered as a pre-medical student when I began college at Cornell University in 1954.

I was also very interested in philosophy at the time and as one could go into medicine in the States without a science degree, I continued to take the more introductory level science courses offered for pre-medical students, along with philosophy. I took the Pre-med organic chemistry course at the same time as I was taking a course in logical positivist philosophy, which was the dominent approach to philosophy in the United States at that time. I found this type of philosophy very arid and stultifying, while the organic chemistry was brilliantly taught and very exciting. I perceived the opportunities it provided for creativity and for synthesizing general principles; the mastery that seemed possible completely engaged me. A kind of game got started between myself and the professor - could he come up with reasonable questions that I wouldn't get right and somehow I did get them right. At the end of the course, I easily decided to become a chemistry major, although I still thought I'd go into medicine.

However, I got completely caught up with chemistry and by my senior year in College, I had great difficulty in deciding between a career in medicine or chemistry. I applied to both medical school and graduate school. I was awarded a prestigious fellowship to study chemistry at Harvard and I decided to do that. However, I had also been accepted to Yale Medical school which I had applied to because it was the only medical school in the US which required physicians to write a thesis. I started at Harvard Chemistry shortly after Watson and Crick had won the Nobel prize for the double helix. I took a course with Watson and one with Crick. I loved the work and did exceedingly well but I became almost clinically depressed about losing the opportunity to become a doctor. I decided in the middle of the year that I really should go to medical school and do medical research rather than pure chemistry. There was something about the relationship between physicians and patients that was really very important to me. My chemistry adviser was a man named Robert Woodward who had also won a Nobel prize - many people thought of him as the most brilliant organic chemist of the 20th century, maybe of all time - but his laboratory was like a factory, very hierarchical, with no chance to interact with him. That certainly diminished my interest.

So I decided to go back to medical school. It was a difficult year of transition. My father died at that point and I needed to earn some money to continue in medical school but I had also exempted out of most of the first two year courses because of my graduate and undergraduate work and I began to work in psychopharmacology at that time.

Who with?

I worked with Daniel X Freedman and Nicholas Giarman. Actually this wasn't my first experience in psychopharmacology. In between graduating from Cornell and beginning graduate work in chemistry at Harvard, I worked for a summer at Lederle Laboratories in New Jersey, searching for new classes of MAO inhibitors.

This was 58?

This was the summer of 1958. I was free to explore their entire library of compounds. Nobody really knew enough about monoamine oxidase or about principles of rational drug design to do anything other than approach this task empirically, but I made some educated guesses which worked out rather well. Through this experience I got caught up with the potential of drugs to treat mental illnesses. I read McIlwain's textbook of Neurochemistry at that point. I developed the probably false notion that all that was worth knowing about neurochemistry at the time could be summarized in 120 pages. This was rather seductive in that it seemed it could be easy enough to learn enough to contribute to this field which was just in its infancy - contrast that with the current situation!

When I began medical school at Yale, after the Harvard experience, I had time to work in a lab for a stipend to earn part of my tuition. I was hired by Jack Peter Green who was studying biogenic amines in mast cells. In my second year, I went on to work with Daniel X Freedman and his collaborator Nicholas Giarman, who was one of the leading pharmacologists of that era but who was killed in an auto crash a few years later.

Dan Freedman and Tom Detre were both assistant professors in Yale at the time and while I had this excellent lab experience with Dan and was thinking more about going into basic science, my first clinical clerkship as a medical student was on Tom Detre's very famous unit at Grace New Haven Hospital, called T 1. Tom was a most talented and charismatic clinician, with a strong interest in psychopharmacology. I was greatly impressed by his way of interacting with severely ill patients. At the end of that 3 week clerkship, I decided that I wanted to be a psychiatrist. I knew that I wanted to continue doing basic research into brain and behaviour but that I also wanted clinical training. This was the final resolution of the dilemma that I became depressed about in college, when trying to decide whether I should become a laboratory scientist or a clinician. What I had found at Yale Medical School at that time seemed to be the perfect synthesis.

What was Freedman like at that time?

Freedman was then a young assistant professor of psychiatry, who was very eager to move psychiatry from an exclusive descriptive and psychodynamic approach to the biological domain as well. However, his basic neuroscience knowledge was limited. I remember that shortly after we met he took me out to dinner to "pick my brain" about the relationship of LSD to serotonin. I remember coming home from that dinner feeling elated, like some important rite of passage had taken place. It was the first time that someone at a faculty level had identified within me an intellectual contribution that I could make. Dan, even then, had the habit of identifying young people who he thought had some promise and then really nurturing them. That would have included people like Jack Barchas, Malcolm Bowers, Floyd Bloom, George Aghajanian, Donald Cohen and many others.

I worked with Dan throughout medical school. He was certainly one of my idols and became and remained very important to me. After my internship, I went to the National Institute of Mental Health in Bethesda, as a Clinical Research Associate in the laboratory of Jack Durrell, which I may return to. After two years at NIMH, I decided that I did not want to stay there permanently. I felt that I would do better at a University, with more independance, than a a junior person in a big lab. I wrote to Dan for a letter of

recommendation. I'm sure it contributed to offers I received from Harvard, Albert Einstein, Cornell and other places. Dan had moved from Yale to the University of Chicago to become the first Chairman of Psychiatry their. Prior to his coming it was a department with no national identity. He had already recruited a number of outstanding people, when I asked him for a recommendation for one of the schools on the East Coast. He said that he would be happy to do so but he asked me to also take a look at Chicago. I accepted out of a sense of politeness. I had no interest whatever in going to the Midwest, which I barely knew. In that era Chicago had a terrible reputation as a city.

I flew into Chicago on a lovely crisp Autumn Sunday afternoon, checked into a University guest center on the Midway, a rather beautiful boulevard lined with campus buildings. I had a few free hours before I was supposed to meet Dan for dinner. I walked across the campus to look through a Gothic cathedral, which seemed out of place. I opened the doors of what is Rockefeller Chapel and the Chicago symphony and Chorus was performing the Bach B Minor Mass. I was absolutely enthralled with Bach at that time and I stayed and listened to it until it was over. By that point I had decided whatever might happen during my visit, I would be agreable to an offer.

Dan and his wife Mary took me out to dinner to their private club. There was an assistant dean, who he had managed to dragoon into spending an evening with this raw recruit. I forget who else was there. They got me slightly intoxicated and the next thing I knew I was calling my wife and saying.. we should come to Chicago. I spent 17 generally very satisfying years there until I could no longer continue clinical research but that is another story.

In the UK, I don't think Dan Freedman has had the impact of someone like Seymour Kety for instance but between the editorship of the Archives of General Psychiatry and his work on LSD he really was one of the seminal figures.

From a scientific contribution point of view, he was significant but not the overwhelming influence that Seymour Kety has been. What was seminal about Dan were the numbers of young people who he brought into research. Any number of leading researchers were considered to be one of "Danny's boys". Its these people, who he mentored and nurtured and, secondly, the standards that he set at the Archives of General Psychiatry, which were his great legacies, more so than his LSD research. He was able to create an aura around the Archives, that Europeans may not have appreciated. People put up with some of the most outrageous things just in order to get their papers published in that journal. He constantly escalated the requirements. He would sometimes get 7 or 8 reviews of a paper,..

Instead of the usual 2 or 3

Yes. People would then begin to write little novellas for these reviews. I recall receiving reviews, which might be 5 or 6 pages each. Of course, there were often significant differences of opinion among the reviewers. Dan would give you some guidance about which points he thought were the ones you should attend to if he decided to accept the paper. There is no question that that became the new standard for the field of psychiatric research. No other journal in psychiatry prior to that time had that level of expectation.

About the time I went to NIMH, Kety produced two reviews in the New England Journal of Medicine and in Science on the sorry state of schizophrenia research, debunking pretty much all that had been done and setting new standards for what should be reliable research designs. In that sense, the achievement of both was complementary - one as an editor, one as an investigator and critic, establishing new standards of excellence.

He worked incredibly hard. He generally didn't come in until 10 or 11 in the morning but then would work till midnight and beyond. He hardly ever ate. He smoked constantly. I probably have increased vulnerability to lung cancer just from the time I spent in his office. Once he started talking to you, it could go on for hours. He would do his editorial work on the journal in bursts - for 2 or 3 days steady, once a month. I think he probably had some mark on the wall behind his desk where he piled the incoming articles. When the stack got to a certain height, he would begin to work it down. He usually dictated his letters and then scribbled corrections on the draft. He had the most incredible, unintelligble scrawl but was blessed with a wonderful typist who could decipher his remarks. I don't know if you've ever had any letters from him or heard any of his talks. Some of it is unintelligible; it almost seemed like he had a thought disorder at times and then sometimes his writings and talks had the most incredible elegance and wit. The editorials he would publish in the Archives could be extremely polished, almost Jamesian, with incredibly complex syntax, puns and multiple levels of meaning. At other times, he could be off-the-wall. and even embarassing. But he really was a great man.

Do you not think its possible that his reputation for his work on LSD has only been temporarily eclipsed because the LSD story went underground and there was no longer any referencing of the work that had been done.

The LSD model of schizophrenia, of course, fell from grace and was replaced by the dopamine hypothesis and in many ways that LSD research pointed towards the 5HT-2 receptors that has certainly been important for my research on atypical antipsychotics.

The other way that Dan was terribly important to the whole field of psychiatry is that he had an immense influence in Washington and among foundations. There is no doubt that he really helped to give shape to the NIMH, as it existed until 1994. He was the eminence grise for so many of the NIMH directors. Herb Pardess would have acknowledged this with great gratitude. Dan and he would be on the phone constantly. I'm reasonably sure he discussed all the major decisions that affected NIMH with Dan. Dan was also constantly testifying before Congress and had great influence among the Foundations. He was the number one consultant to search committees for Chairs of psychiatry and for evaluating existing programs. So, his influence was pervasive and is sorely missed now that there is a real crisis in American psychiatry.

Let me ask you about an earlier crisis first. It seems extraordinary to me that US psychiatry in the 50s and 60s was so controlled by the analysts and yet a few key people like Nathan Kline, Kety and Freedman were able to go to Congress and get them to part with huge amounts of money to set up psychopharmacology research programmes.

Yes. Although American academic psychiatry in that era was dominated by pschoanalysts, many of whom were Europeans who were escaping the war, these people were not narrow minded. Dan Freedman owed his career to Fritz Redlich and while Redlich probably knew little about the biological basis of behaviour, he respected it and really thought that it was important to the future. They did not simply wish to turn their departments into psychoanalytic institutes. I received job offers from a number of these Chairmen, in 1958, who were keen to bring a biological orientation to their departments. There was so much benefit developing from the new antidepressants and neuroleptics that one could easily make a case for increased research in mental health.

Can I take you back to the period at NIMH and ask how that looked to you at the time.

Well, it was fascinating. I had trained in psychiatry at Mass Mental Health Centre, which many people thought had the leading psychiatric residency program in the States. It was an amazing place from 64 - 66, when I was there. It was dominated by psychoanalysts, who were totally committed to psychodynamic psychiatry. Even their approach to schizophrenia was psychoanalytical.

Who were the key figures?

The key figure was Elvin Semrad. He was thought of as the leading spiritual and intellectual light by hundreds and hundreds of the brightest young American psychiatrists who trained there. He had an astonishing ability to establish a relationship with severely ill psychotic patients - to get them to talk about themselves to whatever extent they were capable. He genuinely believed, or so he taught us, that psychotherapy could have a major impact on schizophrenia and that neuroleptic drugs could be a barrier to real recovery.

This was even after chlorpromazine?

Chlorpromazine had been introduced to Mass Mental in the early 1960s. In fact when I was a second year resident, I was appointed chief resident on an on-going NIMH sponsored study to compare psychoanalytic psychotherapy and thioridazine in the treatment of schizophrenia. The grant was for a 7 year project, in which 3 cohorts of very chronic schizophrenic patients were transferred to a research unit at Mass Mental, for 2 years for on the couch psychoanalysis, 4 times per week, - with periods of thioridazine or placebo on a double-blind basis to see if thioridazine had an effect. As I said, I was the chief resident on the 4th year of the project. To cut a long story short, the results showed that psychoanalysis and thioridazine was so superior to psychoanalysis and placebo that the project was terminated at the end of that year. The study proved the drugs worked. However, one could argue that it was never really a clear test of psychonalysis because the people who were administering this treatment, despite being experienced senior analysts, were really participating in this study to meet the expectations of the hospital director rather than out of genuine interest. So they really just went through the motions, often missing appointments and letting patients sleep on the couch.

Who actually conceived of this study ..?

The project was initiated by the Head of the Hospital, Jack Ewalt and the Director of Research, Lester Grinspoon. It had a great impact on any further research in the psychotherapy of schizophrenia.

Philip May did some work in this area as well.

Yes. Phil May did the famous Camarillo State Hospital study, which produced similar finding on the benefits of drugs versus psychotherapy in schizophrenia. What was important to me at Mass Mental Health Center was the opportunity to spend hours listening to and trying to relate to psychotic patients to identify the contribution to their psychosis of their experience in their families and elsewhere. To some extent we were expected to concentrate on "here and now" issues but the main focus was expected to be on childhood. I will never forget presenting a patient I had worked on to one of my supervisors, Dr Susan Van Amerangum, one of the leading figures of Boston psychiatry. I had carefully collected whatever information I could about what had been happening in this patients life at the time of the onset of the psychosis and what was happening in our relationship but the main thing she wanted to know about was the history of his toilet training.

It seems remarkable that an institution as psychodynamically oriented as Mass Mental Health Center was at that time should have produced so many eminent psychopharmacologists, or at least psychobiologists. Eric Kandel and Ed Sachar are striking examples.

On the schizophrenia unit that I described, I participated in research with Ed Sachar who was in the midst of his brilliant work on increased activity of the HPA axis, during psychotic turmoil. Eric Kandel was just beginning his lifelong research on Aplysia. I was assigned to Eric for supervision of one of my outpatient treatment cases. I remember distinctly finding him the most helpful of my supervisers. He was less analytic, as you might expect, than the average person there, but very intuitive and clever. That's the wonderful thing about psychiatry; I don't know how long Eric continued doing clinical work, but he might have done so for some time because it was such an essential part of the identity of a Boston psychiatrist. Clinical skills in psychotherapy were the most highly esteemed. The pressure to become a psychonanalyst was immense. I count myself very lucky that I was able to break away from that culture and go to the NIMH. Many of my fellow residents, who remained in Boston, joined the Psychoanalytic Institute and became training analysts. The potential many had to be scientists was never developed, although there were exceptions, including Richard Shader, Robert Liberman, Roger Meyer, Richard Wyatt, Dan Weinberger, Joel Kleinman, David Reiss and Carl Salzman.

Norman Weiner who became Chairman of Pharmacology at Colorado was at Mass Mental Health as was Joe Schildkraut and Gerry Klerman. Gerry was Semrad's assistant. We didn't have any real didactic training in psychiatric except for a course Gerry was permitted to give on the history of psychiatry. Gerry was the role model for the clinical investigator who was begining psychopharmacology. He was developing the field at the time and publishing in highly respected journals. Although I didn't work with Gerry directly, I knew much about what was going on in his depression research in terms of standardised diagnostic assessments and the collection of biological measures by Joe Schildkraut and others. This certainly influenced me in my later career.

We were supposed to learn it all from our direct clinical work and supervision. I look back on it as both the worst and the best of training. What I most value was the experience of being with patients who were very disturbed and becoming comfortable relating to them.

So, I don't regret having trained there. It's an enormous challenge to do clinical research of the kind that I've done. I've always felt that in order to keep clinical staff motivated over the long run, they have to believe not only in the worth of the science you're engaged in but in you as a clinician. Unless you are a first rate clinician, you will quickly lose their support, which is essential if patients are to participate in research projects. I have heard about examples in research institutes, where staff actually sabotaged the clinical research simply because of their hostility to the clinical chief of the unit, which stemmed from his insensitivity and indifference to patient wellbeing.

When I went to NIMH, Jack Durrell was there. He was considered to be the most outstanding biological psychiatrist working in schizophrenia at the NIMH. He was Seymour Kety's chief clinical investigator. He introduced me to a completely different approach to treating schizophrenia. It violated every single principle that I had been taught at Mass Mental Health Centre. There was no individual psychotherapy. Intensive involvement with the families, different types of group therapies, nurses as co-equals in the treatment enterprise, education about the illness and drug treatment. At first I was horrified by it. I thought that it was almost malpractice. Then, to my astonishment, the first cohort of patients I worked with in this manner improved amazingly. Perhaps, I didn't say it clearly enough when I was talking about Elvin Semrad was that in teaching us to do psychotherapy with schizophrenics, he also discouraged the use of antipsychotic

medicines. When we did use them, it was almost out of a sense of failure, that there must be something wrong with our ability to establish a relationship and to understand what patients were feeling and thinking. What I found at NIMH was the integration of drug treatment with family and social therapy - what we called milieu therapy - with biological research and excellent results. It was really exciting.

Who was responsible for introducing this?

Durrell was. He was a fine scientist and an outstanding clinician. There is no question that that experience shaped my ultimate ability to do clinical psychopharmacology. The psychosocial program I developed for patients on clozapine was all foreshadowed by his example. Ironically, Dr Durrell got into a coneflict with the directors of the Clinical Centre at NIMH. He was told to stop his clinical work and to continue his laboratory work; he refused to do this and left the NIMH. He established the prototype in Washington of what became the Psychiatric Institutes of America, an enormously successful chain of clinics and hospitals. Unfortunately, he never continued his biological research.

After he left, his unit was reassigned to Fred Snyder, a sleep researcher, and I was put in charge of the clinical program. I worked on that Unit for another year and a half. I trained Richard Wyatt and David Kupfer to be my successors. I often said that I came down to NIMH for research training, and I certainly got that, but even more so I learned clinical psychiatry that became the basis for what I went on to do in Chicago and Cleveland.

Beyond what I previously said about the Chicago Symphony and the ambiance of the University of Chicago, the key factor that made me accept Dan's offer to join a brand new department rather than go to a more established place was that I was offered a 12-bed inpatient unit at the Illinois State Psychiatric Institute, with which the University of Chicago had an affiliation. That offered me an opportunity to institute the clinical method, that I had learned at NIMH and provided a base for my research in the biology and treatment of schizophrenia and major depression.

Tell me more about the research there.

Well, it goes back to my first research project at NIMH. I was seeking a neurochemical deficit in schizophrenia. I came across a paper by Hanns Hippius, the Professor of Psychiatry in Munich, in which he and a colleague, Bengzon, reported that schizophrenic patients had increased creatine kinase (CK) activity in their bloodstream. They proposed that this enzyme was leaking out of the brain and that its loss might be the cause of schizophrenia because of the role of CK in energy metabolism. I studied some newly admitted psychotic patients at the NIMH and replicated the finding1. It would take a long time to describe all the studies I did subsequently because I got intensively interested in the mechanism. I was able to show that the form of CK in the blood was coming from skeletal muscle and not brain. I set up various animal models to study the process. The best model that I found for this enzyme leakage from skeletal muscle was the combination of restraint stress plus phencyclidine (PCP) (2).

When I went out to Chicago, I was still very much involved in this study. I was able to get an NIMH grant immediately to pursue it. The Research Unit I set up was to study this phenomenon in the acute stages of psychosis. I had an animal lab also in which I continued to investigate the cause of skeletal muscle damage. This is how I did my first serotonin research because the best model of Duchenne-type muscular dystrophy at that time was the combination of intraperitoneal serotonin plus aortic ligation. I pursued this finding in a great many directions.

I've been a scientist who has followed my intuition fairly freely rather than stay with a narrow research agenda, although I would argue that I have been able to keep my focus but with the freedom to follow the best approach. I think Sol Synder does the same thing. He has told me that he will do 10 experiments for every 1 that really works. I'm not sure what my ratio is but I am willing to take risks.

An interesting result of the neuromuscular work was my discovery that plasma CK activity varies as a function of race. Black people normally have higher plasma CK levels than Causcasians. This was important because relatively small elevations were used to detect the carrier state of muscular dystrophy. Black women were being falsely identified as carriers on the basis of CK levels that were normal for them. I still see this work, which is 25 years old, quoted from time to time.

Gradually though, I got more into the direct study of neurotransmitter hypotheses of mental illness, especially serotonin and dopamine. The critical thing that intervened was that Edward Sachar, who was Chairman of Psychiatry at Columbia at the time, called me to collaborate with him on some neuroendocrine research that might provide a test of the dopamine hypothesis of schizophrenia, by studying basal serum prolactin levels in unmedicated schizophrenic patients and controls (3). We set up a wonderful collaboration that lasted until he had a stroke about five years later. The prolactin work that I did with Sachar led to the first experience I had with clozapine. I was the first to report that clozapine did not stimulate prolactin secretion in man.

I began to pursue a number of independent leads, particularly around the serotonergic system. I developed a whole lot of animal models, based on neuroendocrine effects. That's really what got me into the intensive study of serotonin receptor subtypes from a functional point of view. Another thing that happened was that I was among the first 3 investigators in the US to use fluoxetine to treat depression. The very first patient I gave it to developed a severe dystonic reaction (4). I thought he had received haloperidol instead of fluoxetine, that there had been a nursing error in what he had been given but it turned out that it was fluoxetine. That led me to the study of the interactions between serotonin and dopamine neurotransmission. What I am focussed on now in relation to schizophrenia and depression is still the interaction between the serotonergic and dopaminergic pathways.

So how did clozapine come into your research

A pivotal event was my treatment of a near fatal case of tardive dyskinesia from one of the Illinois state hospitals. This woman was down to perhaps 60% of her normal weight due to her inability to eat on her own, or to be fed by nursing staff due to the severity of her truncal movements and problems in swallowing. I treated her with clozapine which I had permission from Sandoz to use. She really had an astonishing, life-saving improvement in her tardive dyskinesia.

This was when?

I think that would be in the early 80's. This case was the last of many studies with clozapine which led me to work with Sandoz to help plan the strategy to get clozapine approved by the FDA - even on a restricted basis because of its ability to cause agranulocytosis. There was clearly a need for other people who were similarly disabled or who could not respond adequately to the standard antipsychotic drugs to be treated with clozapine.

The prolactin research with clozapine was my first human study with the drug. Before that, I did several studies in animals, which showed that it elevated serum prolactin levels.

Clozapine produced an unusual type of prolactin elevation in the rat. Whereas haloperidol, produced large increases that were prolonged - up to 4 hours - clozapine produced brief increases for 30 minutes of equal magnitude despite the persistence of adequate plasma levels. Gary Gudelsky and I showed that this was due to clozapine's ability to activate hypothalamic dopamine neurones. Clozapine stimulates, for example, large increases in extracellular dopamine in the frontal cortex and to a lesser extent the nucleus accumbens in awake freely moving rats.

A major characteristic of my research style has been to try to integrate pre-clinical and clinical studies. Thus, the patient I described with the dystonia led to my basic research on serotonin and dopamine interactions. Equally there are a number of pre- clinical observations that have generated clinical ideas also. As I indicated, I have done so to satisfy my need to have both in life. It's something I still enjoy. I find it hard to imagine doing clinical psychopharmacology without being really up on the literature of what's happening at the cutting edge of basic research.

There is an argument though that the basic research is begining to take off explosively and it's hard to know just what relevance an awful lot of it has to do with clinical practice. Groups like ACNP and BAP seem to be having problems because the clinical members are going to the meetings and finding that the programme has become almost completely incomprehensible.

That's true. But the clinical person who is really doing something creative has to understand what's happening in basic science. It's less and less easy to do but more and more necessary. That's why I particularly believe in the research centre concept. I was among the first group of awardees of an NIMH-supported clinical research centre when the belief finally surfaced that efforts of that nature shouldn't all be concentrated in Bethesda. The Center I direct started out as a small enterprise and it's still only relatively small but my group has more PhD bench scientists than clinical investigators. I still direct some aspects of the very basic research, usually working with fellows or a fellow, who I can support in the lab to work with one of the PhD's. I would think that without being part of that kind of an enterprise I couldn't keep up with the field.

How many research centres are there in the country?
In the field of mental health, there are now approximately 20 - 25 centers. It started with 7 in 1977. Of the original 7 there are 5 of us left. Each center has its own mission. There is a suicide centre, an adolescent centre, child centres, mood disorder, brain imaging and so on. Mine is devoted to studying the biological and psychopharmacological bases of schizophrenia and mood disorders. The dual focus stems from my earlier work with the neuromuscular system because those kinds of abnormalities were characteristic of both mood disorders and schizophrenia. I'm an anti-Kraepelinian in that sense.

A Unitary psychosis person ?

Yes. While I believe there are clear differences in these disorders, I also find there are many abnormalities that they share in common. My colleagues Helio Elkis of Brazil and Lee Freedman and I have completed a meta-analysis of the literature on CT and MRI scans in schizophrenia, major depression and normal controls. We found essentially no difference between the two patients groups on brain scans. One has to be able to explain these commonalities. However, there are unique features. We've been recently looking at the striatal D-4 receptor abnormality that Phil Seeman reported in schizophrenia. We have partially replicated his findings but we found no such difference in patients with mood disorders.

Let me take you back then to the Chicago. You say that you were there for 17 years, why did you leave?

I left because the governor of Illinois, James Thompson, decided that research in the Department of Mental Health was of extremely low priority. He converted the Illinos State Psychiatric Institute, which had been a well-funded and protected research base, into a community mental health centre. My colleagues and I couldn't continue to do research because of the lack of funds and the clinical burden. When the opportunity was offered to me to occupy an endowed research professorship at Case Western Reserve University School of Medicine, I was ready to accept. I decided Case would provide an excellent environment for the research centre. The move went exceedingly well. However, recently, continued access to in-patient facilities has become a problem. Inpatient research is very costly and requires subsidies from the government or the hospital system. No one wants to pay for it any longer. I believe the research enterprise will suffer greatly because of this.

That brings us back to a point you made earlier about the current crisis in American psychiatry, how do you see that?

We are losing ground in psychiatric research in general, and psychopharmacology in particular. The most serious problem is the amount of money that is available from the National Institute of Health to fund research grants. When NIMH was incorporated into in 1992 or 3, it lost a great deal of money for complicated reasons. Now priority scores have to be in the 10th percentile or better to get funded whereas the 20th percentile or lower was funded at one time. The actual number of grants that are being funded is much less.

The second way in which research is being undermined is the move toward managed care, as part of health reform. Huge insurance companies are gaining control of the medical delivery system. This has cut down the availability of hospital-generated monies for research purposes. Once great hospitals are becoming little different than community hospitals. Only a very select group of academic centers are able to fund a centre that needs an inpatient base to continue. The third way in which research is being cut back is that the pharmaceutical industry is also retrenching.

The one good development, which is something I am very much involved in and proud of, is a non-profit fund raising group called NARSAD - the National Association for Research in Schizophrenia and Depression. I helped to found NARSAD, 8 or 9 years ago, along with Herb Pardes, Sam Keith, Will Carpenter and several other people. Its the first successful means of letting the general public and particularly people of means know that they can, through contributions, really advance the treatment of the seriously mentally ill and our understanding of mental illness.

We started, I remember, hoping we could raise $100,000 to fund 3 or 4 small grants of about $25,000 each. This year we able to provide about $6,500,000, for two fairly large programs. The largest is called The Young Investigators Program and is for people who are just finishing their PhD or residency training and assistant professors who haven't gotten a grant yet. We also have a program for Established Investigators with grants, who are seeking money for some novel ideas that they couldn't get funded at the federal level. I think we now have a national identity, The prospects of getting into the $10 million/year range are really quite good. There isn't any question in my mind that the success of NARSAD has enabled many talented young people to enter and then remain research.

I take a great deal of pleasure in the fact that clozapine is one of the major reasons that wealthy people in the US with children who have serious mental illness have been motivated to contribute to NARSAD. The story I hear over and over again is that after years of unsuccessful treatment with standard drugs that a physician finally put their child or relative on clozapine with excellent results and that out of gratitude and recognition that research does make a difference, they are willing to give substantial amounts to money to NARSAD.

Well that's a good note on which to revisit the clozapine story. At the stage you were doing your prolactin work had it been killed by agranulocytosis?

In 1976, I wrote, what people told me was a very influential review with Stephen Stahl, of the dopamine hypothesis of schizophrenia, which was published in Schizophrenia Bulletin (5). After that, I began to pursue novel drug therapies for schizophrenia. for example dopamine autoreceptor agonists as potential treatments. I studied the effect of alphamethylparatyrosine, an inhibitor of dopamine synthesis. I also began a search for clozapine-like drugs without agranulocytosis. I identified a very interesting drug called melperone (6). Clozapine was going nowhere until 1985 when John Kane and myself and Gil Honigfeld and Jack Singer from Sandoz thought about how an approach could be made to the FDA to gain approval for its use in tardive dyskinesia, based on cases like the one I described previously.

You were able to get hold of clozapine from Sandoz for this lady, how were you able to do that ?

The agranulocytosis was discovered first in 1975 after a group of elderly patients from a small area of Finland died. It was immediately withdrawn from use worldwide. But as is now very apparent, if you withdraw people from clozapine, they may relapse rapidly and severely. We don't really understand why that is but it is a difference from other drugs. It's like taking insulin away from a diabetic. They often won't respond as well to a typical neuroleptic drug as they did. As a result many people were put back on it. Sandoz would probably have preferred to completely end its availability but did continue to provide it on a "compassionate need" basis. I would say myself, George Simpson, John Kane and Nathan Kline were among the few still using it in the US but to a very limited extent. My experience with it was sufficiently positive that I felt obligated to participate in the effort to seek FDA approval. Therefore, Sandoz, with the help of John Kane and myself put together a New Drug Application, which was submitted to the FDA and which was rejected.

By who

Paul Leber and probably others at the FDA rejected the positive recommendation of the Advisory Board to approve clozapine because there was no controlled trial to establish its freedom from tardive dyskinesia. The next step was to provide a controlled trial, which was "Study 30", designed to show its superiority to chlorpromazine for neuroleptic-resistant patient (7). Sandoz was willing to take the considerable risk that clozapine could be shown to be more effective than standard antipsychotic drugs.

They must have put a lot of money into it?

I would estimate that that study must have cost between $5-7 million. Even if it was successful, there was no certainty that the drug would be approved by the FDA or that it would be widely utilized. Other limitations for developing it were that it only could have 5 years of patent life and that Sandoz might be sued if somebody developed agranulocytosis and died. Sandoz also anticipated that it would be used in only a small

number of patients. Fortunately they went ahead with the study and fortunately it was approved.

Why did they go ahead?

Well, I've been told that Sandoz agreed to support the study because the FDA was interested in clozapine, despite or maybe because of their rejection of it for use in tardive dyskinesia. I was also informed that the FDA used its leverage with Sandoz based on non-clozapine related issues to urge them to do this study. So in a very positive way there was a collaboration between the FDA and Sandoz to see that a controlled study with clozapine was done. Not only did that study lead to the approval of clozapine but it showed the potential for other drugs to do as well or even better and it became a great tool for understanding the brain just as did chlorpromazine in its day.

What do you remember most about the trial?

The moment I remember most was the interim analysis which was done when the first 150 patietns were completed. The four principal investigators had a meeting in New York City together with the project statistician John Patin. The results were presented by John and Gil Honigfeld. They showed an astonishing effect of clozapine compared to chlorpromazine. The effect was so strong that even if the two drugs were only equal in effectiveness in the second half, there would still have been a significant advantage for clozapine.

After I returned to Cleveland from that meeting, I called the lab together and said we must drop virtually everything else we were doing and focus on clozapine studies to understand its mechanism. I concluded it was going to revolutionise the field and I believe I was correct in this regard.

When you said that it was going to revolutionise the field, there was a paradox in that, in a sense, it was back to chlorpromazine. For twenty years people had moved down the road of more selective D-2 blocking agents and all of a sudden you've got this dirty drug, which proves superior.

At least for the present, that is how it would appear. Conceptualising what clozapine does clinically, it takes treatment resistant patients and brings them to the level of non-treatment resistant patients. Some people become astonishingly better just as some people with schizophrenia get astonishingly better after haloperidol treatment. However, there are other things that clozapine uniquely does that differentiate it from chlorpromazine such as no extrapyramidal symptoms, no tardive dyskinesia, no prolactin elevations, and I think most importantly it improves some aspects of cognitive function (8).

You've stated we need to draw a distinction between the antipsychotics and the neuroleptics. Do we?

I think so. The capacity to produce parkinsonism and akathisia are major and immense drawbacks for an antipsychotic agent. Probably as much as 50% of schizophrenic patients under routine treatment conditions become non-compliant within months of starting medication. Most people believe that's due to extra- pyramidal side effects. So an antipsychotic drug which doesn't produce them is going to be so much better tolerated. There's all sorts of evidence to suggest that continuous rather than intermittent treatment with neuroleptic drugs is going to lead to the best long term outcome. Therefore, you have to have a drug that doesn't produce intolerable acute side effects or delayed onset

side effects like tardive dyskinesia. Some day we're going to have antipsychotic drugs that does this.

The other neuroleptics are effective across a range of disorders, the major affective disorders, OCD, is clozapine any good for conditions other than schizophrenia ?

Clozapine is quite effective in a range of disorders. We have published several reports showing that clozapine is effective in treatment-resistant manic depressive disorder and treatment resistant psychotic depression. We've also confirmed that it's very effective in l-dopa and bromocriptine-induced psychosis in Parkinson's disease. It probably doesn't help OCD; in our hands, it makes OCD worse. There are actually some older studies using clozapine in classical major depression as an anti-depressant and it was effective.

So, we are back to the unitary psychosis concept.

To some extent yes. I've recently written a paper about the implications of psychopharmacology research for the unitary psychosis hypothesis. The fact that drugs like clozapine are effective across the spectrum of mood and schizophreniform illnesses, is supportive of this view.

How does it work, if it isn't working by blocking D-2 receptors on their own

Well I've provided a lot of valid evidence, in my view, that blockade of the 5HT-2 receptor is an important element but I no longer believe that all of its advantages are due to that property. I think there could be a significant contribution from 5HT-6 and 5HT-7 receptor antagonism, possibly D-2 and D-4 receptor blockade and possibly its ability to modulate the cholinergic system. Other investigators highlight its strong alpha-1 and -2 adrenergic blocking activity. Clozapine is the ultimate "dirty" drug of psychopharmacology, at least for the present, and that may be its genius.

If that is the genius where does that leave us. The industry at the moment is predicated on purer and purer drugs. Molecular biology and receptor cloning is all about getting a drug that will target just one receptor system

That strategy has much to recommend it. We do need drugs that are incredibly selective for obvious reasons. They are indispensable but clearly, in the case of schizophrenia at least, they may be less effective as drugs. There is much evidence that strong 5HT-2 and weak D-2 receptor blockade, as is present in risperidone, sertindole and olanzapine is useful to decrease extrapyramidal symptoms. However, I believe that these drugs will show significant differences from each other and clozapine. They will have very different clinical profiles because of the differences in their relative affinities for receptors other than the 5HT-2A and D-2 receptors.

The catecholamine theory of depression and the dopamine hypothesis of schizophrenia really made the field respectable but did they also hold things back.

They provided a structure and the hope that we were on the right track. It has turned out that the original versions of these hypotheses were seriously in error. They sought to explain too much. That is particularly true for the catecholamine hypothesis. Its amazing how long the dopamine hypothesis was not seriously challenged given all that we know to be incompatible with it.

One of the hunches that I have on that was the industry is highly conservative and once they start on a line of drug development - to inhibit catecholamine or 5HT

reuptake or to block D-2 receptors - they keep doing that and that keeps a theory in place even though the field should have actually moved on.

I remember attempts in the 80s to move beyond the catecholamine hypothesis into the endorphines and the opiates as well as an attempt to develop drugs related to GABA as antipsychotics. But the failure to find anything of therapeutic value brought the field back to dopamine. An early version of the serotonin hypothesis of schizophrenia, as explored in the 50s and early 60s, died because of the failure to validate any evidence for psychotomimetic indoleamines in urine and blood or postmortem specimens from schizophrenics and the absense of gross effects on the behaviour of schizophrenics of enhancing and dimishing serotonergic activity.

Would you have needed to have that validation. You could argue that the LSD model had much more face validity than the amphetamine model - after all housewives were having amphetamines during the '50's and they weren't going psychotic

I may be less than objective here but my feeling is that psychopharmacology really drives the field. There's a great scepticism about the biological abnormalities reported in schizophrenic patients, particularly in this era of neuroleptic treatment. And besides that, there is the enormous problem provided by the probable heterogeneity of etiology and pathophysiology. We all give lip service to this issue but then many people proceed to forget it and keep expecting to find group differences between schizophrenic patients and controls. I wrote a paper once on sub-typing of schizophrenia and how to use this concept to study the biology of schizophrenia. The heterogeneity view suggests you must follow single cases or small groups of cases, which may be biologically similar. Once you start to examine a whole consecutive series of schizophrenic patients for common biological deficits, you're bound to find great variability.

The biological marker strategy has proven exceedingly difficult to work with for this reason. I'm sure its one of the things that makes the search for a genetic marker so appealing. In order to find a principle if you will, from psychopharmacology that is as sustainable as was the dopamine hypothesis has been is very desirable. For example, as we speak, there's a lot of interest in the possibility of a specific novel dopamine abnormality in schizophrenia, in the D-4 system. This stems from Seemans' research which was stimulated by the demonstration of the greater effectiveness of clozapine versus typical neuroleptics schizophrenic patients rather than from animal research. I'm convinced that animal models of "schizophrenia" are of secondary value. Schizophrenia is the quintessential human brain disease. It is going to be exceedingly difficult to obtain a useful animal model. We can model certain components of the disorder, i.e. stereotyped behaviour or catatonia, but the essence of the disorder, the cognitive dysfunction and loss of volition, is very hard to model in animals. One can use animal work to generate hypothesis but these ultimately have to be proven in man.

Before clozapine, you were systematically working your way through the options in terms of treatments active on dopamine receptors but with clozapine a real passion seems to have entered into the picture for you.

That's true. I had treated individual cases through the years, maybe half a dozen, that had responded exceptionally well to clozapine after doing poorly with a variety of treatments. But it is a tribute to the power of the randomised control trial, as I said, that only when I saw the outcome of the first half of Study 30 showing the superiority of clozapine over chlorpromazine was I truly convinced that it was exceptional enough clinically to push forward with it and secondly that it was urgent to study the biological

basis for this. This re-directed my energies and eventually led to the serotonin hypothesis of its mechanism of action.

Serotonin has been an enduring interest, along with dopamine- serotonin interactions. The first major breakthrough that I had in this regard was understanding the basis for the time course of clozapine-induced prolactin increases in rodents. The prevailing idea about the mechanism of action of clozapine was that D-1 receptor blockade was the important feature. I tried to check that hypothesis by studying other atypical antipsychotic drugs. At that point in time I had used a variety of antipsychotic drugs, which had atypical properties in man - I'm not sure if many other people had as much experience. So I could approach it on the basis of both clinical experience as well as the basic research I had been doing. I also had the advantage of having the extensive statistical support provided by the clinical research centre. A research fellow from Japan and I, Shigehiro Matsuhara of Hokkaido University, were able to study about 20 putative antipsychotic compounds with D-1, D-2 and 5HT-2 activity. Ultimately we were able to show that we could an identify an atypical antipsychotic drug on the basis of the D- 2/5HT-2 model.

For a long time, I believed that all the clinical advantages of clozapine had to be due to one biological mechanism. I rejected the possibility that its spectrum of advantage for treating both positive and negative symptoms in the absence of tardive dyskinesia, EPS and prolactin increases could be due to many different receptor affinities in the right balance. Now I have reluctantly come to think that this possibility may be correct. I now believe that there are multiple mechanisms that clozapine directly or indirectly calls into play, which account for its advantages.

Clozapine has clearly transformed the way you see things and it has given hope to a great number of people but you still seem very open on the issues. You encouraged me at one point to seek publication for an article asking whether we can we afford it. A lot of people, in your position, approached by someone like me who really hadn't had the opportunity to see the benefits you had seen, might have tried to kill the piece.

Well I must say that I didn't try to kill it or encourage you not to seek publication because I felt that there was a need for debate about the issue. Under some clinical circumstances, the greater effectiveness of clozapine could cost so much that one could rationally say that it's not worth it (10). I'm not so fanatic about seeing patients do better that I think there's no limit tp the amount of money that should be made available for what might be a small advantage. There are health systems that might provide excellent care for schizophrenia in which clozapine might not be a cost-effective treatment. I think one of the great deficiencies in psychiatry right now is that there are too few people studying cost effectiveness issues.

Can we do it? We're being forced to but can it validly be done?

Oh I think we can. My son, David, has an MD and a PhD in economics. He did his PhD with Gary Becker of the University of Chicago, who won the Nobel prize in Economics in 1992. I've just seen a paper that David co-authored on the cost effectiveness of prostate cancer testing. He's a real professional at it, I am strictly an amateur. But I see the way that it could be done if people had the proper training. I realise that the approach has an enormous amount to recommend it but the methodology, as it applies to psychiatry, is still rather limited.

One approach would be a cost utility study which I think is the best approach to apply to schizophrenia. In a cost utility model, different people who have a stake in the issue, whether it's the patient, the family or society, indicate measures of value. This might be

the number of years of one's life you'd be willing to sacrifice in order to be free of the symptoms and social dysfunction of schizophrenia. This approach to pharmaco-economics works best in a very complicated situation like schizophrenia, where there are many off-sets to a particular advantage. That approach, if it were applied to antipsychotic drugs would allow schizophrenics, who I think often provide reliable judgements, or their families, to say how much it is worth, for example, to have freedom from the risk of tardive dyskinesia versus the possibility of getting agranulocytosis, seizures or increased weight gain, on the negative side.

With that approach, given the greater cost of clozapine, we could come up with how much we would be willing to pay for each unit of utility, each meaningful increment in benefit. In a world where the rationing of health care is becoming more prevalent, there are crucial decisions that should be made on the basis of that kind of information or similar considerations.

Now to get back to my personal style, why would I encourage someone with a different idea to publish? Actually, I've always had the feeling that if I was wrong about something, I'd rather discover it myself. In that sense, encouraging somebody else to produce something that's different to what I believe would be somewhat inconsistent. The only reason I might have been tempted to discourage you would be my passion for clozapine. I really think it's grossly under-utilised and I would not like to have it under-utilised for the wrong reasons, one of which is the idea that it isn't cost effective.

The cost-structure of the English health care system, however, is entirely different to the American one. The costs that are attached to the treatment of mental illness in England are almost an order of magnitude lower than in the US. If that's really how little it costs to treat schizophrenia in England, then you have to respect that it may not be a cost effective treatment. But that is not the case here in America. I have completed another study in which I have looked at the cost of treating the non- treatment resistant schizophrenic patient versus the ones who are treatment resistant. I can still show a cost effective benefit of clozapine in non-treatment resistant schizophrenia, although its very slight compared to what is possible in treatment resistant cases, which are extremely expensive to treat in the United States.

In the case of England, one of the things that I think is relevant is that in a public sector model, there is this great tendency to under-estimate the cost. The full costs are hidden from the public. I almost think it's deliberate. It's the exact opposite in a private sector model where for financial reasons, both for maximum reimbursement and to lower taxes, the public and private sector are motivated to overestimate their costs. In the study that I did, I had to use what I considered to be unrealistically low figures of what it cost to treat a patient in the public sector because they wouldn't really charge any of the administrative costs for running the system. I think that is the case in England, where many aspects of running the health services are hidden, so that it looks like an amazingly efficient system.

One of the curious consequences about the issue of the cost of clozapine is that in the UK, at least, one of the things you hear people say is that it was only with clozapine that psychiatry began to be taken seriously - because of its costs.

Because of the costs! That's appalling. Nevertheless, if that is what it takes to be taken seriously, I'll accept it. There are amazing stories in the States about the impact of using clozapine. One of the low or high points, depending on your viewpoint, was that I was chairing a symposium, just as clozapine was being introduced, at the annual American Psychiatric Association meeting in New York City. There was a ballroom full of people at the Marriott Marquis Hotel, 2-3000 people. John Strauss, of Yale, had just started to speak. All of a sudden, the doors of the auditorium opened. In streamed about 150

people from the New York Chapter of the National Alliance for the Mentally Ill screaming, "clozapine is obscene", carrying banners and completely disrupting the meeting because they were so upset about the price of clozapine. They wouldn't let Strauss continue. I somehow got the leader of this group, a man named David Jaffe, to quiet down by making an agreement with him that if he would wait until the talk was finished, I would give him time to address the audience. There were police gathering at that point and it could have become an ugly scene at any time. Jaffe got his group under control and Dr Strauss finished. Then Jaffe got up and gave a really passionate speech about how because of the price at that time, many people who wanted it weren't going to be able to get it. He got more than a polite round of applause from the audience and then left.

I don't expect that I will ever do anything else in my life that would be nearly as gratifying as the work I did with clozapine. I have had many experiences along the way with people whose lives have been transformed by it. A patient of mine, whose picture was on the cover of Time magazine several years ago, was a street person who had been in jail and who is now the produce manager of a supermarket in my neighbourhood. He's engaged and living a very satisfactory life. There are a lot of people in the first group of patients we started on clozapine who have not been hospitalised in 9 years. To be a part of that is what I dreamed about as a College student.

However, I am very mindful that we are far from doing what we need to do with regard to serious mental illness. My goal right now is to study the phase of schizophrenia prior to the appearance of psychosis. I believe that there is a neurodegenerative process that is taking place at that crucial time.

That might be picked up by screening?

That's what we're working on. We think we can do it. We are intensively working with patients and families to recapture the events of that time. I believe there may be some process that may involve stress-induced glucocorticoids and probably glutamate in some way, to cause a condition called apoptosis - progammed cell death. This is only thing that we know of at this point that would explain how you could have a degeneration of neurones without there being signs of gliosis. The brain is re-modelled during adolescence. Ironically this was pre-figured in my neuro-muscular work. I saw evidence that there had to be a dying back of neurones to explain what we had found plus a sprouting of other neurones to recover the function of the muscle fibres that were left. Even then, I wrote that it might be possible that some process like this could be happening in the central nervous system. This now seems a possibility. It turns out that all the 5HT-2/D-2 compounds are causing effects on CK activity in psychotic patients, not all of them but a surprisingly substantial number of them. So maybe I'm going to have a chance to go back and hopefully finish up the story where my career started.

Are we talking about something like a nerve growth factor as being important in the treatment?

Well, lets say if there is this process of neuro-restructuring that has gone awry in schizophrenia, then a variety of factors that guide neuronal connections could turn out to be very important. In the case of the cognitive dysfunction that may be central to the disorder, the majority of the damage may be present at the time of the first episode. This suggests a need to identify and treat patients before they present in the emergency room in a delusional, hallucinatory state. I believe that the positive and negative symptoms emerge from the cognitive dysfunction. Because of this, we have been doing a lot of work on pre-morbid function in people at risk for schizophrenia. Some aspects of that process could be modelled in animals. We know that neuronal loss takes place during very early adolescence, before most people become schizophrenic; most of the

remodelling in the brain is supposed to be over by ages 12 or 13. But it's probable that a small but significant part continues later. This is based really on a theory which was developed by Peter Huttonlocher, at the University of Chicago. It has never been adequately studied in primates or rodents. If that's when pathology is begining in schizophrenia, our animal research should focus on it like "a laser beam".

From the outside it seemed that with DSM III, the psychiatric profession changed and went biological but with Clozapine on the front cover of Time as well as Listening to Prozac, this change of culture has reached down to street level. Would this be a fair statement?

Biological psychiatry never took over the field as much as one would think. We may have been very visible in terms of the media but if you ever attended an Americian Psychiatric Association meeting, you would realise that the majority of American psychiatrists are more interested in psychotherapy and the like. Someone I know, with a history of recurrent depressions, recently suicided; prior to her suicide, she was treated by one doctor with psychotherapy and another doctor with drugs. That reflects the old bias against drug treatment. The psychiatrist who did the psychotherapy wouldn't use drugs because he didn't know enough about them or thought it would interfere with their relationship

How can that attitude remain despite the work of someone like Klerman to show that the psychotherapy and drug therapy can be additive?

Yes but you have to understand where the prestige is. Tom Detre used to say that society sees us as druggists. And at Mass Mental Health Centre, the goal was not to be become an academic, or do research in a laboratory, or do clinical trials, it was to be a psychoanalyst. What's really transforming this situation is the way mental health care is being structured by huge insurance companies and managed care, who will pay physicians only to do pharmacotherapy. They fund 10/15 mins with a patient once a month for a review of drug treatment. They will not pay adequately for psychotherapy. That will be funded only by someone being willing to pay for it out of his or her pocket. That aspect of the psychiatrist's professional life will diminish greatly. The American medical student is turning away from psychiatry because of poor reimbursement and because they don't want to do just pharmacotherapy.

I am concerned that the rate of progress in the next several decades is not going to be the same as what we have had in the past. The next generation of psychiatrists is going to be much smaller. It's a rather pessimistic view but I do think you are on the right track in chronicling what has been a really golden age of psychopharmacology. I hope it's going to continue in some way in the future because there is still so much to do. Clozapine and the other new drugs are a real advance but they are only paliatives. My goal is to stop this disease before it ever expresses itself. If I can achieve something toward that in the next decade, I will really feel very fulfilled.

REFERENCES

1. Meltzer HY (1968). Creatine kinase and aldolase in serum: abnormality common to acute psychoses. Science 159: 1368-1370.

2. Kuncl RW and Meltzer HY (1974). Pathologic effect of phencyclidine and restraint on rat skeletal muscle structure: Prevention of prior denervation. Experimental Neurology 45: 387-402.

3. Meltzer HY, Sachar EJ and Frantz AG (1974). Serum prolactin levels in unmedicated schizophrenic patients. Archives of General Psychiatry 31: 564-569.

4. Meltzer HY, Young M, Metz J, Fang VS, Schyve PM and Arora RC (1979). Extrapyramidal side effects and increased serum prolactin following fluoxetine, a new antidepressant. Journal of Neural Transmission 45: 165-175.

5. Meltzer HY and Stahl SM (1976). The dopamine hypothesis of schizophrenia: A review. Schizophrenia Bulletin 2: 19-76.

6. Metzer HY, Fang VS and Young MA (1980). Clozapine-like drugs. Psychopharmacology Bulletin 16: 32-34.

7. Kane J, Honigfeld G, Singer J, Meltzer HY and the Clozaril Collaborative Study Group (1988). Clozapine for the treatment-resistant schozphrenic: A double-blind comparison with chlorpromazine. Archives of General Psychiatry 45: 789-796.

8. Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D and Meltzer HY (1993). Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biological Psychiatry 34: 702-712.

9. Meltzer HY, Matsubara S and Lee J-C (1989). Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pKi values. Journal of Pharmacology and Experimental Therapeutics 251: 238-246.

10. Meltzer HY, Cola P, Way L, Thompson PA, Bastani B, Davies MA and Snitz B (1993). Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. American Journal of Psychiatry 150: 1630-1638.