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IN MEMORY OF MARTIN M. KATZ (1927-2017)

Contributions to INHN

Edited

by

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IN MEMORY OF MARTIN M. KATZ

(1917-2017)

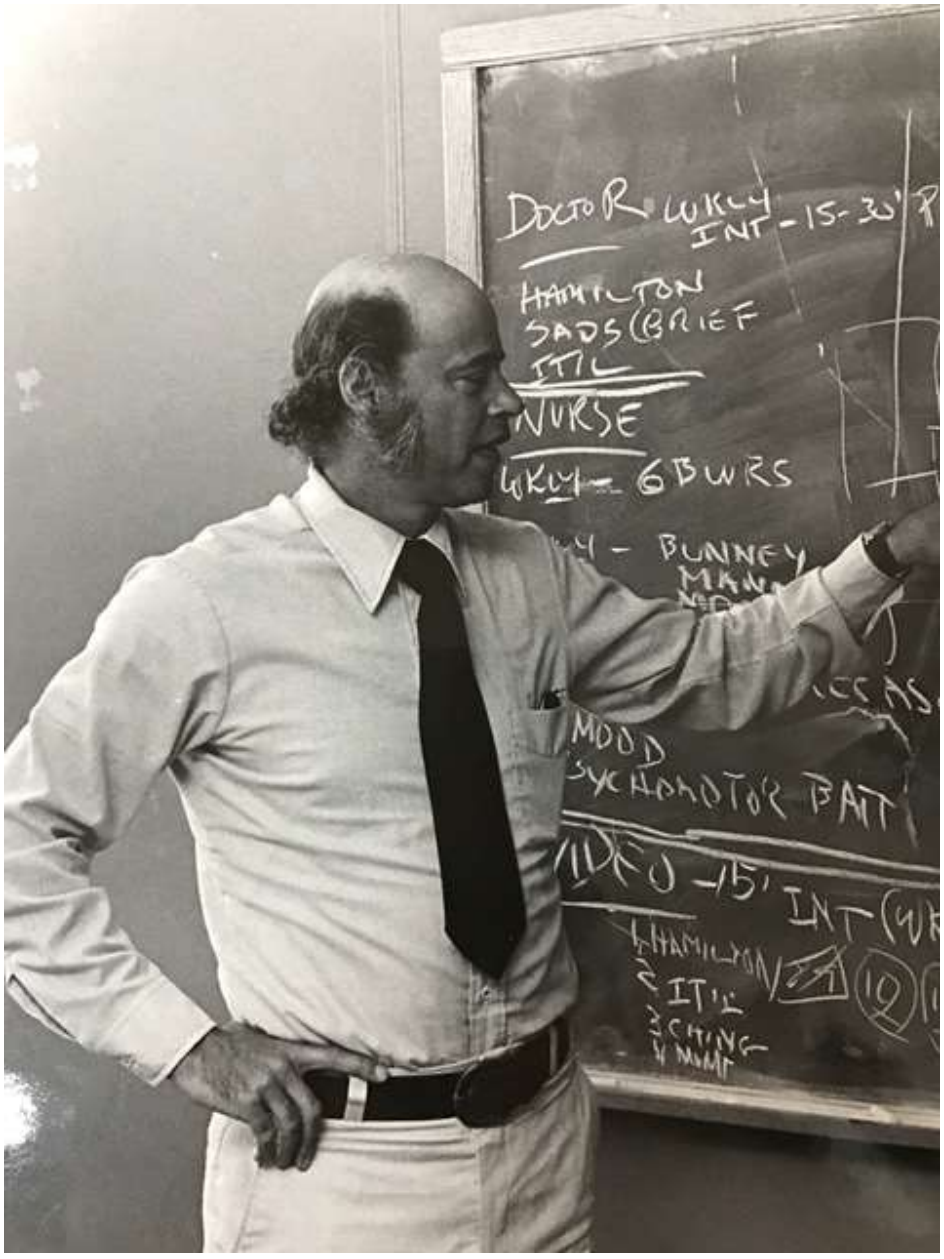
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Photo taken in December 2016 by Nancie Katz.

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In Memoriam: Martin M. Katz
by
Thomas A. Ban

On January 12, 2017, Martin M. Katz, passed away in Rockville, MD, at a nursing home. He was 89-years-old.

The eldest of three sons of a haberdasher and a sales woman, Martin M. Katz was born on August 6, 1927, in Brooklyn, New York. He received his A.B. in Chemistry and Psychology Brooklyn College, in 1949 and his Ph.D. in Clinical Psychology and Physiology from the University of Texas, in 1954. His postdoctoral research that ascorbic acid improved cognitive functions in malnourished Latino children, attracted attention and in 1957 he was recruited for the position of Executive Secretary of the first Psychopharmacology Advisory Committee of the National Institutes of Health. The Committee was instrumental in establishing the Psychopharmacology Service Center (PSC) of the National Institute of Mental Health (NIMH) to facilitate the development of psychopharmacology at the time a new field and he was to become one of the first members of the staff of PSC. It was during his tenure at PSC that he developed and introduced the Katz Adjustment Scales for measuring clinical and social adjustment in the community of patients discharged from hospital after successful pharmacological treatment (Katz and Lyerly, 1963).

To pursue his interests Katz set up a laboratory at the National Institute of Mental Health (NIMH), in the mid-1960s to study the effects of "psychedelic drugs," developed a "video-methodology" for the study of psychopathology in psychopharmacology and explored the effect of culture on the manifestations of psychiatric disorders, spending a year at the University of Hawaii (Katz, 1970; Katz and Itil, 1974; Katz, Sanborn and Gudeman, 1969). Then, in 1968, he was appointed Chief of the Clinical Research Branch (CRB), a new Branch at the Institute with the mission to stimulate research on the causes and treatment of schizophrenia and affective disorders. A key event during his tenure at CRB, and a turning point in his research interest was the Williamsburg Conference (1969), which highlighted neurochemical theories about the pathogenesis of depression and brought to attention that progress in depression research would require the identification of better clinical end points and the development of suitable clinical methodology for testing relevant biochemical hypotheses (Blackwell, 2011). To meet the needs a Collaborative Program on the Psychobiology of Depression, was launched that laid the groundwork for large scale testing of the

biochemical hypotheses of the time about the genesis of depression (Katz et al., 1979). Katz leadership of CRB was recognized by the. Administrator's Award for Meritorious Achievement, Alcohol, Drug Abuse and Mental Health and Human Services, US Government, 1979.

After leaving the NIMH, Marty became Co-Director of the Field Research Center of the World Health Organization in Hawaii before joining academy, in the mid-1980s, first as Chief of the Division of Psychology, then as Director of Experimental Psychopathology and professor in the Department of Psychiatry at Albert Einstein College of Medicine and Montefiore Medical Center. During this time (1984-1994) he was also the Principal Investigator for NIMH funded research on the Psychobiology of Depression that focused on the "measurement of depression" and on the timing, specificity and prediction of antidepressant effects (Katz et al., 1987; Marsella, Hirschfeld and Katz, 1987). He continued with his research well into the 2nd decade of the 21st century at the University of Texas Health Sciences Center in San Antonio. Furthermore, as an octogenarian he became one of the major contributors to the website of the International Network for the History of Neuropsychopharmacology, an educational network.

Marty's contributions are crowned with the publication of two monographs in the last three years of his life in which he shows that deconstructing the diagnosis of depression, uncovering its dimensional structure and developing a methodology that allows the measuring of drug induced changes on the independent dimensions that comprise it could open up a new perspective in the clinical development of drugs for the treatment of depression (Bowden, 2016; Katz, 2013, 2016.)

Katz was intensively involved in the activities of the American College of Neuropsychopharmacology (ACNP) for well over 50 years. He was elected a member of ACNP in 1963 and in the years that followed, he was a member of various Committees, served as Vice-President, in 1977, played a prominent role in launching Neuropsychopharmacology, ACNP's journal and edited History of the ACNP, Volume 10 of ACNP's Oral History series, in which the first fifty years of the College was documented (Katz, 2011). For his contributions to the College, Martin Katz was the recipient of ACNP's 2016 Paul Hoch Distinguished Service Award. By that time, he was terminally ill. He did not have the strength to attend the Award Winning Ceremony at the 2016 annual meeting of the College. It was his son, Pete who collected the Award for him.

Left to right: Alan Frazer, Pete Katz and Raquel Gur. Photo taken in Hollywood, Florida, in 2016 at the ACNP annual meeting (Pete Katz is showing the annual Paul Hoch Distinguished Service Award received by Martin M. Katz). Photo received from Nancie Katz.

Marty Katz survived by his wife, Barbara Gelb Kathy, two children, Nancy and Pete and two grandchildren He will be dearly missed by his family, friends and the neuropsychopharmacology community at large.

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INTERVIEWS OF MARTIN M. KATZ

INTRODUCTION

Marty Katz was interviewed three times at annual meeting of the American College of Neuropsychopharmacology. The first interview was conducted by Jean Endicott, on December 14, 1995, in San Juan, Puerto Rico; the second by Stephen Koslow, on December 10, 2007, in Boca Raton, Florida; and the third, two days later, on December 12, 2017, by Thomas Ban at the same meeting.

The interviews were transcribed and edited, and the edited interviews were included respectively in volumes 4, 9 and 10 of An Oral History of Neuropsychopharmacology (Katz 2011 a, b, c.).

There was a further edit of the interviews before including them in this memorial volume.

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MARTIN M. KATZ

Interviewed by Jean Endicott

San Juan, Puerto Rico, December 14, 1995

JE: I'm Dr. Jean Endicott and I'm interviewing Dr. Martin Katz, who's been a member of ACNP since 1963. Now, Dr. Katz, what field did you start out in?

MK: I got my basic education in chemistry, went into psychology in graduate school and received my degree in psychology at the University of Texas. So, I had an interest in these two disciplines for quite a while.

JE: How did you get into your current field?

MK: Into psychopharmacology?

JE: Right.

MK: After graduating from the University of Texas, I worked there for a year on research as a post-doctoral fellow. The project had to do with the effects of Vitamin C on intelligence, a study I was very skeptical would result in any positive results, but it was a nice position. I had run into Jonathan Cole at a scientific meeting in Texas, and he was impressed with the design of that study, because it was so much like a drug study. He was on the verge of taking over a large program at the National Institute of Mental Health on a new discipline called psychopharmacology, so he was seeking people who had done things like this or might be interested in that field. That was the last I saw of him for a while. But shortly after completing that post-doc I went to Washington to work in the Veterans Administration Neuropsychiatric Laboratory. There I got involved in a project evaluating the outcome of psychotherapy and worked with Maurice Lorr, who was expert in development of quantitative rating scales for symptomatology. This is back in the late 1950s, and was a new research area at the time. And, I came across Dr. Cole there again. It turns out he was in charge of something like a two-million-dollar project by way the National Institute of Mental Health to promote this new discipline of psychopharmacology. All this happened because of excitement over the discovery of the new drugs for schizophrenia that was provoking a revolution in our field. They apparently wouldn't give him enough money to get that program started. I was viewed as a young researcher, but I had the skills he was interested in. He was hiring people, so he brought me to NIH. I was recruited in 1957 as the Executive Secretary of the first

Psychopharmacology Advisory Committee. I must have been thirty years old at the time and I was confronted with relating to all these senior scientists in the field from all over the country. So, it was a very exciting prospect.

JE: What was the reaction to having a psychologist head of that?

MK: I don't think there was any concern. These were the people going to put this new field together so the committee was made up of representatives from several disciplines. Psychopharmacology, by definition, involved psychiatry, chemistry, pharmacology and psychology, so the mix of people involved was from all of these fields. They might come from whatever direction in the sciences. That was not unusual.

JE: What were some of the first programs you were involved in?

MK: The entity was called the Psychopharmacology Service Center (PSC) and the mission was to get out into the field and to develop this new discipline. That meant providing investigators with funds to develop programs in basic research on the new drugs and, in a parallel fashion, to attack the problems of clinically evaluating the new drugs. Despite knowing the drugs worked and, having seen them do so in small studies, they needed definitive evidence on large representative samples around the country that the drugs were effective. So, the second part of the program had to do with what they called Collaborative Multi-hospital Clinical Programs for the evaluation of these new drugs. To Jon Cole's credit he was able, with the help of his staff, to launch these studies. They were the first collaborative studies ever launched by NIMH to investigate this kind of issue, which is the evaluation of psychiatric treatments. So, the Center staff had to be concerned about issues in both basic and in clinical research.

JE: Do you remember who some of the people in the field were back then?

MK: The Chairman of this advisory group was Ralph Gerard, a nationally known neurophysiologist from the University of Michigan. In psychology, it was Howard Hunt, Columbia University. In biology and psychiatry, it was Seymour Kety. Nathan Kline, a clinical researcher, was one of the real movers in the field; he helped generate the funds for the program. Louis Goodman, Chairman of Pharmacology at University of Utah, was the author of the most prominent text in clinical pharmacology. These were much respected people and they were, because of the funds and new opportunities, as excited as everybody else about this field.

JE: Could you tell us something about what your career was and what you did in relation to that?

MK: I was Executive Secretary, which meant active involvement in the review of grant applications and support of some research programs in my area of work. Then, after almost two years in that position, I went back into active research at the Center. I worked with the collaborative programs that had begun to develop methods of evaluation. I was given the task of developing a methodology for evaluating the long-term effects of these agents once the patients when they went back into the community; how long did the early positive effects last. That was a major issue and I developed a method for measuring clinical and social adjustment in the community. They were called the Katz Adjustment Scales and they're still in use. On an analogous issue, there was short-term evaluation of the drugs. Having come out of the laboratory in the VA, I was very familiar with those techniques and helped put them together for that large-scale study. So, I worked on that part of the study and also on issues around psychedelic, LSD type drugs. These drugs were also a major issue. When the field started we had this parallel development of "good" drugs, the tranquilizers and antidepressants, the ones supposed to solve mental disorder, and "bad" drugs, the psychedelics. The latter were capable of disrupting the "personal psyche" and the whole community. I was given responsibility for following up on those drugs, accumulating scientific evidence on their actions and impact. After doing that for a few years, I was appointed head of a special studies section for psychopharmacology. It gave me the opportunity to develop a laboratory that would look more intensively at LSD type drugs. With a small staff, I developed a laboratory in a prison to look at new methodologies for studying how they worked. At first, for safety, we experimented with small dosages to see the early psychological effects. Later we expanded these studies and managed to get a number of other investigators involved. So, this research grew into a major program, in parallel to what was going on in the community, with funds increasing every year. I was heavily involved from about 1963 until 1968. Then I was able to follow another interest I had, the influence of culture as a variable in drugs effects, and more generally as a factor in the expression of abnormal behavior.

JE: Expression of abnormal behavior?

MK: Right. Also, I got involved, by way of that special studies group, with the broader issue of classification of disorders. We mounted a very large national conference in 1965 that resulted in a book on *Classification of Mental Disorders* designed with Jonathan Cole and Walter Barton, who was head of the American Psychiatric Association. That national conference identified some of the major problems confronting the field with regard to diagnosis, which I would be involved in later.

JE: What were the drugs that you worked with, other than LSD? Were they mainly antipsychotics or were you, also, involved with the antidepressants?

MK: During the 1960's mainly antipsychotic drugs. I had done a lot of work on the phenomenology of schizophrenia, on the effects of drugs on schizophrenia, by way of the quantitative rating methods developed during that time. That was my main area of work. Then, in the studies with LSD we used amphetamine and chlorpromazine as controls. Those lines of research ran parallel, they didn't cross.

JE: Were you using videotape technology back then?

MK: No. I wasn't involved with that at that time.

JE: So, you moved into the issue of cultural expression and the response of different ethnic groups to treatment. Could you say something about the project?

MK: I spent 1968 at the University of Hawaii in Honolulu on a Fellowship from the Mental Health in Asia and the Pacific Program. I took some of the rating methods we'd developed for clinical drug trials to apply to the issue of whether psychosis in Hawaii-Japanese and Hawaii-Caucasian schizophrenic patients was expressed differently in symptoms and social behavior. Hawaii was a great laboratory for examining the effects of ethnic influence on behavior, so it was part of the reason I was sent there. We worked out a research program for doing that at the State hospital. We started research and I did get involved in videotaping about that time, because we were attracted to the possibility of demonstrating the differences in pathology in a more open way, so that people could see it more clearly than by just extracting information from the scales you and I are very familiar with. I was there for a year; greatly stimulated by the East-West Program on Mental Health in Asia and the Pacific. The NIMH, in the meantime, had changed structurally, under a new Director. Psychopharmacology became a branch. The new NIMH director was Stan Yolles, and they had redesigned how they were going to support research in the future. As part of the reorganization they created a new Clinical Research Branch and had a chief of it for about a year. He, however, ran into some difficulty and decided to leave. This was a new branch with a whole new mission. Lou Wienckowski, who was the director of the division of extramural programs, offered me the position of Chief of that branch which brought me back from Honolulu. That branch had a direct line to psychopharmacology, because what psychopharmacology had accomplished was to make us all aware we had to do a better job of evaluating treatments. It

sounds very strange, and you'd think we were well equipped to do that kind of thing by then. But it was the sixties and there were very few people who had a strong psychometrics orientation or who were in a position to develop the kind of instruments capable of sound tests of whether one treatment was better than another. The kind of background I had made it easier for me to go into the general field of clinical research. Psychopharmacology still figured strongly but in clinical research proper we would have to look at the world differently. The broad field of clinical studies was partitioned into a program on depression, one on schizophrenia, a program on psychosocial treatments, a program on basic psychopathology and one on biological factors in mental disorder. After I became Chief of the Branch, we developed "focused programs," as for example, the program on depression and psychosocial treatments. Then we began programs in psychopharmacology that had thrusts in two directions. We had to promote and support investigators in the field who could develop methodologies we needed and also promote the general field of clinical research. To do that we had to stimulate the field by way of conferences and support of collaborative research. In many ways, it was a direct extension of what we had been doing in psychopharmacology. I never left psychopharmacology as a specialization, I just extended my interest. I still came to the ACNP meeting every year, regardless.

JE: When you took over as head of the Clinical Research Branch, do you remember what the budget was?

MK: It must have been in the area of about $5 million.

JE: And that was the period when it was growing fairly rapidly.

MK: By the time I left, which was ten years later, it was somewhere in the range of twenty to twenty-five million dollars, so, it had gone up rapidly during those years. Those were good days for mental health research. Psychopharmacology had a lot to do with stimulating support for all areas of our field and we appreciated that. In that 10-year period we had several stimulating conferences. In 1969 there was the well-known Williamsburg Conference, which highlighted depression and the very exciting work on neurochemical theories of depression, the so-called catecholamine hypothesis of affective disorders identified depression as a derangement of central neurochemical systems. The work had grown out of psychopharmacology, because the discovery of antidepressants opened up the issue of how these drugs were working. The drugs appeared to be changing functioning in certain neurotransmitter systems and investigators were able to associate the changes with depression. It looked as if we were very close to learning what the

biochemical source of the depressed condition was. But you couldn't arrive at a definitive answer unless you did clinical studies, which were sound methodologically, and had the proper breadth and reliable diagnostic information. So, it raised the question of how to achieve a clinical study with a sufficiently large and diverse sample to test the biochemical hypothesis. And the need for such a study was one of the conclusions of that conference. But, the real issues identified as important to resolve, before the field could go forward, were three. One was confusion over diagnosis. At that time, there were several diagnostic systems and people argued about them continuously. You couldn't compare the results from one study to another because of the different diagnostic systems they used. Out of that discussion came a recommendation that we develop a more reliable nosological system for research purposes. The second issue had to do with pursuing ideas about the genetic basis of the disorders, and the third had to with testing, in a definitive way, the exciting neurochemical hypotheses. From that meeting, where we had some of the best minds in the country, a set of recommendations were developed with the idea that we generate a collaborative study. But before that occurred, something had to be done about upgrading the methodology to be used, particularly for diagnosis. You might remember this very well because you were one of the key figures we turned to. After the meeting, we asked Bob Spitzer and your group, with Eli Robins, from St. Louis to "collaborate" and clear up the methodology relevant to diagnosis.

JE: Believe it or not, we did.

MK: First we had to refine the "Research Diagnostic Criteria", because we wanted to have diagnoses that met research standards for reliability so that a clinician in Iowa wouldn't be collecting data in a different way than a clinician in New York. So, you and your group were commissioned to develop a standardized data collection instrument. After getting that done, if we had stopped we would have accomplished a lot, because those instruments you, Bob Spitzer and Eli Robins developed, the RDC and SADS, have been used by almost all investigators for the past twenty years. It upgraded quality and helped make collaborative studies possible. Now we could proceed to test ideas about the neurochemistry of depression and the role of genetics. We organized another conference on the psychology of depression so we could better study the principal theories and psychological phenomena in depression. That also was a successful conference and was followed, as was the biological conference, by a published book. The title of the first book on the Williamsburg Conference, edited by Williams, Katz, and Shield was, *The Psychobiology of the Depressive Illnesses*; and the title of the second book, edited by Friedman

and Katz was, *The Psychology of Depression*. Later on, we attacked the whole issue of psychotherapy for depression and compared it directly with drug treatment through a collaborative study, published in an article by Waskow et al in the Archives of Gen Psychiatry. What I'd like to point out about those initial studies, The Clinical and the Biological Collaborative Studies on the Psychobiology of Depression, was that they were the first collaborative studies. There's a question now whether similar studies will ever get done, designed to test experimental hypotheses. At that time, we were familiar with the type of collaborative study intended to evaluate a treatment. We had a format for that. But we never used the methodology for a study that would go beyond treatment to test theoretical hypotheses about the causes or nature of a major mental disorder.

JE: There were other differences, too. Most collaborative projects were designed in Washington and carried out across the country. And the way you set up these new programs, there was a lot of back and forth deciding what was going to be studied. Could you describe some of that?

MK: We would bring our group of scientists and clinicians, leaders in the field, together, and they would have responsibility for designing the study. We had the staff to help and people of substantive background at the NIMH who could collaborate in the design and the work, but their status in the group was as co-investigators. The group would design the project and participate in carrying it out. To use the Collaborative Biology Study as an example; we had the expert in neuroendocrinology at one center who would take care of the laboratory work for the six participating hospitals, whereas measures of central nervous system chemistry were handled in another laboratory. The investigators who ran each study were leaders in the field, people like Peter Stokes at Cornell and Jim Maas at Yale. In St. Louis, the group would be using the most advanced equipment, mass spectrophotometry, for measuring drug concentrations in the plasma. At that time, there were only two or three pieces of that type of equipment in the entire country. The St. Louis group and Eli Robins would take responsibility for that work. We would, in Washington, take responsibility for the behavioral analysis. It was in that biological study that we instituted the video method, so that we had a pictorial record, based on the standard interview you promoted earlier for data collection. Since these assessments would be done frequently in the drug evaluation process, we developed a much briefer, simpler interview for the video work. But every patient would get the same standard interview at each assessment point. We intended to create a psychological testing instrument out of this, a standardized instrument interview and rating procedure that would be administered pre, during and post the course of drug treatment. This was a new technique added to the standard instruments, the Hamilton scale and SADS-C. So, that's the

way the biological component of the collaborative studies was conducted. Its parallel was the clinical study which investigated nosology and genetics, and had as complex a collaborative arrangement as the biological study, involving investigators from all over the country. We were quite proud of those studies. They had a lot of effect on research if you examine its impact on the scientific community, apart from the study's actual results. In a sense, the collaborative network and studies served as mechanisms for psychiatric and research training in our field. While we didn't have that many centers in the country, they could train a large number of investigators. The field was still young at that time and we like to think that people like you, Nancy Andreasen, Paula Clayton, Bill Coryell, Martin Keller, Jim Kocsis, Alan Swann, Regina Casper and Steve Secunda could go on to be leading investigators in our field. So that was a major plus for the program in a field that needed improvement in the quality of its methodology to solve the major clinical and scientific problems that confronted us.

JE: You also had skeptics who thought that it was going to be impossible for groups of independent investigators to work in a collaborative fashion. But the fact is those programs are still running.

MK: That's right. We were thinking about that at the recent memorial for Gerry Klerman, Chairman of the clinical study. Unfortunately, we also lost Jim Maas who was the moving force behind the whole biological effort. In the talks at Gerry's memorial, we realized that the leaders of these two groups had to be strong people to manage investigators who were independent leaders in their own right. The co-investigators were all very accomplished and they weren't used to working closely together with other people, who they viewed more as competitors than collaborators. So, the strong leadership qualities that were necessary in a Chairman were certainly fulfilled by Gerry Klerman and Jim Maas.

JE: That was planned, on your part, carefully.

MK: You make a lot of mistakes, but in those cases, we chose well. You and I know that the clinical study wouldn't have lasted three or four years if we didn't have somebody like Gerry at the helm. I feel the same way about Jim Maas who was at the helm on the biological aspects of the study.

JE: You were chief of the Clinical Research Branch of NIMH during that time.

MK: As Clinical Research Branch Chief, over that ten-year period, there was another accomplishment we were proud of. Toward the end of that tour, we managed to establish the

Clinical Research Center Program. This was a kind of program the NIH supported for almost all medical specialties but we did not have one in mental health in the early 1980's. A lot of people were very skeptical about it being a worthwhile venture. It seemed it would require large amounts of money for very broad programs of research and training when the NIMH was used to putting money in very specific, focused research programs. The latter could be monitored more easily, more effectively. But we also knew the side effects of creating these unusual programs where we were in great need of trained investigators. We needed people to have more room to develop so those centers would be a little more expensive, but we would get a lot more people into the field and a lot more problems solved. And it did work that way. I understand it is now being phased out, but I think it did great service for the development of our clinical research program for the past twenty years.

JE: I hope it's not over.

MK: I think it's close to being over because of budget constraints.

JE: What have you seen as major changes over the past twenty years in your work and contact with people?

MK: That's a difficult question but you can look at it from the standpoint of what hoped might be accomplished and what has actually happened. When we look back over the field, we see that by the early sixties, almost all the major drugs we have today had already been developed. The class of tranquilizers for schizophrenia, the class of antidepressants for depressive and anxiety disorders, lithium for mania and maintenance of bipolar depressions were all available. These were revolutionary developments. Previously there had been very little effective treatment for schizophrenia and we were losing hope. Regarding depression, we were very skeptical in this country that the disorder had anything to do with biology. It was viewed as the most psychological of our illnesses and, suddenly, these chemical agents came along and appeared to resolve in a matter of a few weeks, a condition that previously lasted a year or two. Even the psychologists, the skeptics like us, who came from the other side of this theoretical controversy, were convinced that this as a real impact. Those were major developments. The expectations were very high, that we were on the verge of getting to the sources of mental disorder, their biological basis. We began to think they were all biologically based and it would just be a matter of time until we understood how all the drugs worked. That was because all of the effective drugs were discovered accidentally but we would now be designing and creating new drugs which would be more effective, faster and

so forth. We thought all of these new developments were around the corner; we would just stoke the furnace a little, put more money in the field and get it done. And, as the field mushroomed, there were many more investigators, and much more money for development. If you look over the past thirty years, a lot has happened; plenty of drugs appear somewhat better, but until the introduction of Prozac (fluoxetine) in the early 1980's, nothing really remarkable happened. Now, some people feel these newer drugs are remarkable and I can go along with part of that, but I don't think it's the kind of development we saw with the first wave of new drugs. That's a long time between breakthroughs. Secondly, we thought that the roots of mental disorder would be uncovered and we would be able to link biological variables to mental disorder directly. In other words, we would have "biological markers" for the disorders to an extent that when a patient walked into an interviewing or examination room and had blood taken there would be a test to tell us if this patient was schizophrenic or depressed. That hasn't happened. Not only hasn't it happened, we have yet to find a biological marker for any mental disorder that can be used in a diagnostic or predictive sense. Thirdly, the mechanisms of action underlying how these drugs bring about recovery are still clouded. The theories are very interesting, but we don't have definitive answers and it may be the reason we have not been able to develop new, revolutionary, drugs. On the other hand, a great deal has happened. We have struggled with these issues in the biological study of depression over many years. We're disappointed in a lot of what we were not able to find. On the other hand, we have found a few things through our work. The idea that antidepressant drugs don't impact the illness until two or three weeks pass, that widely accepted notion, is not quite true. We found that a lot goes on in the beginning that wasn't measured. The assumption of a delay is based on the fact that the drug didn't change depression as a whole without acknowledging that it did change aspects of the syndrome, for example the anxiety or anger level, very early. That may sound a small thing to make a great deal of. When investigators felt nothing happened for two or three weeks, they moved away from the notion early actions of the drug on neurochemistry were the key to antidepressant effects. So, they started to look later in the treatment process, opening up a whole new field of inquiry. We feel they abandoned, too quickly, looking at the initial stage of neurochemical changes. A lot of this controversy comes about because of the diminished role measurement of behavior has played. For some reason, behavior receded into the background with the introduction of all this exciting biological methodology. The fact that you could get a new discipline like molecular biology or neuroimaging applied to our field raised the excitement level so much that the whole area of behavior has been neglected. Jim

Maas and I worked very hard on trying to conceptualize this state of affairs that led to misdirection. We made the point that drugs don't work specifically on a disorder. That isn't part of the drug language. The language of the drug is to affect certain systems in the body, which result in changes in behavior that are specific and are going to get related to mental disorder. But the issue really is relating changes in neurochemical functioning to specific actions on behavior. We argued for trying to think in terms of neurochemical components in the action of drugs, rather than in terms of their action on disorders and diagnoses. But if we go to the trouble to get down to such refined intricate biological measurements we should be doing the same thing in the sphere of behavior.

JE: Phenomenologically.

MK: Right, if we want to solve that problem.

JE: So, where do you think we're going?

MK: We've all gotten a lift from the fact that studies that went on for thirty years to do with measuring neurotransmitter metabolites in CSF or urine or plasma, were all attempts to measure what's going on in the brain indirectly. It was very difficult work and it made some progress. But the real steps will be taken when we can measure brain functioning directly. With all the advances, we should expect to see a little more rapid movement now. It appears to be moving along a little bit faster. If the behavioral side can be handled better in the future, by utilizing experts who can do this work carefully, we'll be able to connect up a lot more quickly in the future. What we want to know about the source of mental disorder is how does it come about? We have to acknowledge that although we have thousands of research articles we haven't quite got there yet. We know very little about the biology of the disorders and that's the big issue. The other big issue is how these drugs work, because the future rests on whether we can resolve that question. If we can understand how they work, knowledge will move in two directions, in one direction it will tell us more about the key facets underlying a disorder. That was the great hope. And in the other it'll allow us to use this behavioral compartmental model that's been available for ten or twenty years, to target transmitter systems. As we'll be able to do that more efficiently and more successfully, we'll be able to manipulate behavior much more easily. I do want to say something about one of the disappointments of the last thirty years and that is about the "bad" drugs, the LSD-type drugs I spoke of in the beginning. Those who remember that era, recall what a wild era it was. From the standpoint of NIMH, we used to have people come to see us, perfectly sound, established investigators, who had ideas of putting these drugs into the water of Jack Kennedy and Khrushchev

to bring peace in the future and so forth. They had seen the light. Of course, we worked with these people, because there had been wild ideas before and some worked. But this movement frightened the field and, in the course of it, we left these drugs rather early. There's not much we could have done about that, because they were potentially very harmful. But anyone who saw the impact these drugs had on the mind, from a psychological point of view, had to feel we were knocking on the door of a better understanding of what goes on in the brain. These drugs produced remarkable changes in ideas, perceptions, and images, given in a dosage almost invisible to the naked eye. Yet, somehow, we couldn't quite get a grasp on them that would allow us to learn enough to move on in a way that would have an effect on science. We watched the drugs get buried under an avalanche of bad publicity and bad effects. Not that we could afford to let their indiscriminate use go on, knowing how much damage they can bring about. But drugs that have that kind of power should not have been abandoned. I'd say that is another lost venture.

JE: A kind of a missed opportunity.

MK: We have, in some way to be able to open that door again, without losing control of the potentially harmful things associated with it.

JE: Were there other points you wanted to make about the history and your role?

MK: I'd just like to say that I consider myself very lucky that through a fortuitous set of events I wound up in that job at the PSC at such a young age and got to see so much of what was going on in the country and the world. I was in a favored position for many years to watch this whole field of neuropsychopharmacology develop. When I left after a span of time in psychopharmacology and clinical research, I became a Professor at Albert Einstein College of Medicine for ten years. I tried to develop a new program in psychology that would take advantage of the different ideas from the different disciplines I came across. But this is an era in which everything seems to be to be more constrained, pulling back, so we've got to be patient and maybe it will open up again at some point. That's the story.

JE: Thank you.

MARTIN M. KATZ

Interviewed by Stephen H. Koslow
Boca Raton, Florida, December 10, 2007

SK: I am Stephen Koslow interviewing Doctor Marty Katz for the International Archives of the American College of Neuropsychopharmacology. I am going to ask Doctor Katz to address his life, career and the impact that he has had on the field and the ACNP. To start with can you give us an introduction to your life?

MK: I was born in Brooklyn, New York and grew up there. I received my degree at Brooklyn College, majoring in chemistry and engineering, but switched over to psychology after coming back from the Army. The shift was partly because it was determined I was color blind and had difficulty with titration and other lab operations in chemistry. My first interest then was in combining these two fields. Psychology was very exciting at that time and was just beginning to develop as a science. After I completed my undergraduate experience I went on to the University of Texas where I took my degree in psychology, with physiology as a minor. With that kind of background, I received my PhD in psychology.

SK: What made you interested in adding drugs to the formula?

MK: My first job right out of graduate school, where I had been studying the interaction of self-esteem and memory, was at the Texas Women's University. It was for a post doctorate year as an assistant professor. The school was run by a Dean who was an expert in physiology and nutrition science with grants from many sources which provided support for my position. In a very nice way she said we had a wonderful grant from the Florida State Citrus Group Commission; they were interested in the effects of vitamin C on intellectual functioning. I felt that was very intriguing but would not qualify as a serious experiment. But, she convinced me I could be a great help to the chemist and nutritionist if I would design a study on the effects of Vitamin C on intellectual functioning in children. She had a couple of grade schools where kids who were nutritionally underfed could have their ascorbic acid levels raised by orange juice every morning. In the kids who were nutritionally well fed it was believed that increasing ascorbic acid would not have an effect on their nutrition or performance so they could have the same orange juice which would act like a "placebo." Since the kids didn't know who was nutritionally deficient and who was not, and

everyone had the same treatment, it was like a "double blind" study. The expectation was that kids at an adequate level of Vitamin C would not be improved by the orange juice, but the ones that were deficient, would. I thought this was an interesting idea, but too far out to be taken seriously. Strangely enough, the results showed the kids who had the lowest ascorbic acid level that was increased by the orange juice supplement, had a significant improvement in their performance IQ tests six months later. It shook me up a bit and I developed more respect for the effects of nutrients and chemistry on behavior in children. Later, at a regional research conference, I related this story to Jonathan Cole.

SK: Who was Jonathan Cole at that time?

MK: Jonathan Cole was just about to become the head of the new psychopharmacology group at NIH. The Congress had agreed to give the NIH two million dollars because of the introduction of chlorpromazine for the treatment of schizophrenia and the excitement around that. It was the beginning of the psychotropic drug era and they were hoping to stimulate that whole field into more research in psychopharmacology. Jonathan, in his creative way, saw the Vitamin C experiment as a kind of double blind drug study and carried that thought back with him to Washington. A year later, I took a job in the Neuropsychiatric Research Lab at the VA in Washington, to study the efficacy of psychotherapy which was my main interest at the time. It turned out to not be very satisfying but I learned a lot about the technology of evaluating change in mental patients. Strangely, in the nineteen fifties, psychiatry and psychology didn't know how to evaluate treatments. They had been experimenting for thirty years with open studies that did not have proper controls or adequate methods for measuring change so there was no definitive test for a treatment. But now a model had to be developed to deal with the introduction of this new drug to the field. When Jonathan offered me a position at NIH, I was very reluctant to take it because I didn't want to continue in government. But, I did look at the Institute and was overwhelmed by the nature of the NIH operation. It was, for scientists, a thing of beauty. It had wonderful laboratories in which scientists were able to work on the problems they considered important, and in this new program, were the new drugs that would change psychiatry and the treatment of mental disorder forever. I immediately perked up and realized I was being offered something very, very good.

SK: So, you were being recruited to do research on psychopharmacology?

MK: I was being recruited to help the NIH develop collaborative clinical trials of the new drugs. So far, they had only very small studies demonstrating effectiveness, so what was needed was a large-scale study across the country of chlorpromazine and variations of it in schizophrenia. Jonathan Cole was in charge of developing this major study and he needed help with the development of methodology and research design. My association with the collaborative study was only part time. My real job was working with a Psychopharmacology Advisory Committee initiated by the NIH that was made up of leading scientists in the country from many disciplines. They were to establish this new science, and to guide the development of the field.

SK: Do you remember who some of those people were?

MK: The chairman was Ralph Gerard who was a world-famous neurophysiologist. He had started an Institute of Mental Health at the University of Michigan, and was a very interesting figure. The people on the committee included Seymour Kety, who was the head of intramural research at the Institute of Mental Health when I was there. Sam Greenhouse, a statistician and expert on the design of clinical studies, Nathan Kline, probably the leading proponent of the new drugs in the treatment of schizophrenia and mainly responsible for generating that two million dollars for research, Lou Goodman, a famous figure in pharmacology and author of one of the outstanding texts in that field, and Lou Lasagna, a great pharmacologist then at the University of Rochester. They were some of the most impressive people I have ever come across and I was in my late twenties at the time. I was to be the executive secretary working with Ralph Gerard, the Chairman; essentially, I was the administrator of the operation and still very wet behind the ears. I was also overwhelmed in the presence of such great scientific figures. They must have thought I was pulled from the ranks of some prestigious scientific society because they treated me with all of the respect I didn't deserve. I had that job for two years and Jonathan Cole and the staff managed to get those collaborative programs started and obtain the funding for a wide range of basic and clinical research in the field.

SK: Were the collaborative programs all on schizophrenia or also in other research?

MK: They went beyond schizophrenia, for mental disorders generally. But, the first successful drugs in treating mental disorder were the ones in schizophrenia. By nineteen- sixty the antidepressant drugs made their entrance as did lithium. These drugs came in a wave and we witnessed a small revolution in the whole field of psychiatry and the treatment of mental disorders.

SK: So, this was your first foray into psychopharmacology and initiating major research programs at the Federal level. Was this about the same time the ACNP started and did you get involved with the ACNP?

MK: The year it started was 1961 and I became a member shortly after that, in ’62, or ’63. I wasn’t a founding member but I was one of the first. The society was quite small at the time and had relatively high standards for membership based mainly around the great clinical drug developments and basic work underpinning it. It was very well balanced in terms of basic and clinical work and seems very different from today where the balance has shifted well over into the basic area. The clinical side seems to be much more reduced, but at that time it was central to the society’s action and mission. One of the people on the Advisory Committee I didn’t mention on the clinical side was Heinz Lehmann, who introduced chlorpromazine to North America. There were all these famous people around and it was an inspiring time.

SK: What other significant things did you do that were important for developing the field of psychopharmacology?

MK: I worked in the field of psychopharmacology directly for a ten-year period with Jonathan. I went from assisting and doing research on the collaborative study to development of clinical methodology for drug evaluation, a particular skill that I had. I was assigned to develop methods of measurement of long term, rather than short term effects, of the drugs. Out of that came a set of adjustment scales that have been widely used since and were used to study the effects of drugs on schizophrenia a year later. I put extensive time into that involvement. My other assignment was in research on diagnosis and I was asked to develop a national conference aimed at shoring up the standard diagnostic system in psychiatry, which was very wobbly. There were many systems at that time, and much controversy about which one was better. There was no such thing as an operationally based system, there were several clinically based systems related to different theories and clinicians would just be comfortable with one or other system. So, we tried to develop a scientific approach, one that would be acceptable to clinical investigators, and would meet research standards. We couldn’t worry about the whole field of administrative, practical and clinical demands, but we had to worry about diagnosis for research, because, as scientists know, the results of any one study are only relevant to the kinds of patients in the study. If they can’t be defined in a systematic and precise way, nobody knows who the treatment is effective for and the results cannot be generalized. We were aiming toward a system for diagnosis based on operational

definitions. I was given the job of creating a conference on the state of the field and the problems preventing the development of this new system. The conference was called the Role of Methodology and Classification in Psychiatry and was international in its scope. In the course of it I developed experience in putting together large conferences. We had some formidable people at those meetings. I remember Max Hamilton, famous now for the Hamilton Depression Scale, being at that first meeting and other important figures from Great Britain, other countries and the United States. It resulted in a volume that had some impact at the time, published by the government. The volume was called *The Role of Methodology and Classification in Psychopathology and Psychiatry*, co-authored by myself, Jonathan Cole and Walter Barton, executive director of the American Psychiatric Association. That conference was a success and we like to think it played a role in research over the coming years which eventually led in the mid-1970's to the development of the current DSM classification scheme. On another track, during the late 1960s, we initiated a special studies program at a nearby prison and conducted experiments designed to test new methods in "normal subjects" for the evaluation of the effects of LSD and other drugs. That program lasted several years. People like Irene Waskow and Carl Salzman, who was just out of residency, participated. I had started out, when I first moved into psychopharmacology, studying these kinds of drugs and my first paper on the psychological effects of LSD type drugs was at a symposium at the Army Chemical Center in Maryland, way back.

SK: Was that one of your most significant papers?

M.K: I don't think it created great waves. LSD is, even today, somewhat of a mystery. What it does to the mind is very difficult to describe in any sensible way although lots of people have tried. LSD has a great impact on various psychological functions, as remarkable in the chemistry of brain function as chlorpromazine, but from an entirely different direction. But we have never been able to study it in the way we would like because of all the problems it brought with it, the untoward effects and the possibility of permanent harm. These things scared people off research and the government stepped in to shut down most of what was being done. So, a great mystery remains; decades later we still do not have any answers. We did turn out a couple of important papers, one published in the *Journal of Abnormal Psychology*, back in the 1960s. We also did work on tetrahydrocannabinol and set up new methodology for the psychological study of these drugs. We added to the little objective knowledge on their psychological effects. We developed perceptual methods and questionnaires that were designed to test these exotic drugs and one of them is still

used today. So, the laboratory did make some valuable contributions to our current knowledge base.

SK: You were there at the introduction of all the significant psychotropic medications and treatment regimens for mental disorders. What else did you do while you were at the federal government to move these areas forward?

MK: The work I did intensively was, for example, the application of behavioral methods to articulating the clinical and psychological components of schizophrenia so that we would learn which aspects the drugs affected. We were able, in the collaborative studies, to describe the classification of schizophrenia in a different way, in accord with a behavioral typology. This was intended to make the diagnostic system amenable to determining which types were helped by which drugs. I didn't get to into depression research during that period, because I focused my research on schizophrenia and the psychedelic drugs. These directions were interrupted in 1968 when I went on a sabbatical year from the National Institutes of Health to the East-West Center in Hawaii to pursue another interest. That had to do with a very different kind of problem; the impact of culture in shaping the pathology of schizophrenia. Jonathan Cole was moving on and things were changing about what course psychopharmacology would take at the National Institute of Mental Health. I wasn't sure I wanted to remain at the Institute; I was ready to move on. What occurred, however, was that the Institute was reorganized and a new branch was established that several of us had promoted. It was a more broadly-based group designated as the Clinical Research Branch. Many of the staff thought that the psychopharmacology program had been instrumental in creating methodology that was needed for study all treatments of mental disorders. The program had moved the whole field forward, not only the drug field, but every aspect. We were now ready to attack all the problems in clinical research, not only the behavioral aspects, but the role of neurochemistry in the nature and etiology of the disorders. The study of the neurochemistry of depression and schizophrenia could proceed on its own, not necessarily associated with drugs. The Clinical Research Branch was to be dedicated to studies of the basic psychopathology and treatment of all mental disorders, apart from those which continued to evolve in the drug world. The new branch had a chief who stayed for the first year, then because of some conflict with administration, had left. Louis Wienckowski, a formidable leader at the NIH took over the division of extramural research under Stanley Yolles, the director of NIMH, and offered me the position. It was a wonderful opportunity to get involved in a whole array of new research problems and I

was only too eager to move up and take it on. So, when I returned to the Institute in late 1968, I took on that new responsibility and position.

SK: How long did you stay in that position and what were your most significant accomplishments during that period?

MK: From 1968 to 1978 and we did some remarkable things. We took the collaborative strategy designed to evaluate new drugs over to basic research and applied it to study the psychobiology of depression. The big problem in clinical research is that the subjects of study are human beings. The kind of research we did required large samples, not like in the laboratory, and you can't get those unless you dedicate yourself to five or ten years of accumulating data and overcoming, at the same time, many practical obstacles. We learned from the early drug studies that the collaborative mechanism could help get beyond these obstacles. Soon after I got there we convened a national conference on the biology of the depressive disorders. New theory had postulated a neurochemical basis to depression; it was viewed by many at that time as highly speculative. Depression was a disorder recognized for centuries and all of us who studied it in the pre-drug era accepted it as a terrible illness, but were convinced that its roots were 90% psychological, brought about by developmental dysfunction, specific environmental stresses, or variations on these themes. The idea that chemistry could create depression and changes in chemistry could resolve it, was viewed as a pipe dream, a notion that lacked any substantive base. The drug revolution changed that whole idea, and out of that came some very fruitful hypotheses about chemistry and depression. The Williamsburg conference, held in 1969, took on all these issues and came up with recommendations for the kind of research that needed to be done in the future. So, in a way, the conferees, the experts from various disciplines were providing my new Clinical Research Branch, comprised of psychiatrists, psychologists and pharmacologists with a guide to what could be done in the future if we had the resources, the backing of the Institute and the energy to pull it off. Fortunately, we had the right people at the right time to create these collaborative studies. One area, biological studies, was chaired by Jim Maas, one of the classic scientist psychiatrists of his day, a formidable man. He would take on the testing of biochemical theories, and as part of that program put together the first experiment to include the proper controls, a wide range of methodology, and the large patient sample required to test hypotheses about chemistry and depression, utilizing the collaborative mechanism. I don't think there are many examples like that in the literature because it required a range of investigators, the very large patient sample, several hospitals and great expense. It seemed too unwieldy to pull off but a lot of

innovative people made sure the thing worked. It took people like you Steve Koslow and Steve Secunda, a psychiatrist in private practice today, as well as Tom Williams who coordinated the Williamsburg conference and enlisted a number of very unusual people to participate. The Biological Studies program represented one side of our overall effort, the Clinical Studies Collaborative program, represented the other. The clinical study was chaired by Gerry Klerman. That study saw as its first task the development of an objective, reliable diagnostic system in which categories would be operationally defined, in accord with the Research Diagnostic Criteria of the St. Louis school. That had to be our first step in testing new biological theories or in researching the nature of depression; to generate a system for diagnosing and classifying disorders that was generalizable, one that when used in research would guide the selection of patients, and make the results applicable to patients at large. So that had to be done immediately. We then contracted with Jean Endicott, Bob Spitzer and Eli Robins to refine the Research Diagnostic Criteria, the operational criteria they created that formed the basis for the DSM system. Bob Spitzer became the chairman of the DSM Committee for Psychiatry the following year and created the first operationally defined research diagnostic criteria system applicable to the whole field of psychiatry. You see, we are very modest; we take credit for all of these things!

SK: During your career, you have done a lot of things; your publications include classification, diagnosis, psychopharmacology, methodology of assessing behavior and the cross-culture area. Do you want to comment about those areas as they relate to your general interest in mental disorders and quantification of psychopathology?

MK: I do want to say something about the cross-cultural study because it does link to these other fields; although it may not seem on the surface to do that. It is an old interest of how cultures impact the development of mental disorders; for example, how Japanese schizophrenia is different from American schizophrenia. It's hard to show this and to see what the real factors are without doing the research and one of the contributions of the adjustment scales for evaluating the long-term effects of drugs was part of this. I had been asked to create that method to study the social adjustment of patients with schizophrenia a year after they had a drug or some other treatment so we would know how well they were functioning in the community. In so doing I developed a way of describing abnormal behavior in people, in language amenable to a lay person, so you could describe the pathology of a patient just as it appears in the community. It would not be through the eyes of the expert but through those of a lay person. Based on my earlier interest I developed that so it could be applied in different cultures to get an idea of what the everyday behavior of a certain

kind of abnormal person was in that culture. Then we could use it to compare the everyday behavior of different ethnic or cultural groups. The laboratory for doing that research was in Hawaii where they have many different ethnic groups well represented. They are all very different, Japanese, Filipino, Native Hawaiians, and Caucasians. We set up a research program for studying these groups to show the differences and similarities in social behavior across "normal" and mentally disturbed subgroups. The method provides a view of how people related in the community, going beyond what a doctor sees in 15 minutes or half hour interview, and how the drug treated patient appears a year later. The method worked very well with regard to these issues and was eventually carried over to the World Health Organization epidemiological studies. I also worked with the World Health Organization in a study that compared schizophrenia in Japan to Nigerian, Indian, and Hawaiian communities. We published an extensive report in the *Journal, Culture, Medicine and Psychiatry* in 1987. At that point, I had to leave the field because of other pressing involvements. But it was all part of the same fabric; one gets interested in the interaction between culture and behavior and then the interaction of chemistry and behavior. When we talk about mechanisms of action of drugs it leads me to this other area; the continuing problems which surround the clinical trials of new drugs. What is meant by behavior in these clinical trials is the range and number of symptoms that are measured on a Hamilton Depression rating scale. That type of study tells us nothing about the profile of drug-induced behavioral effects. In the collaborative studies, we were able to make links between neurochemical drug actions and behavior more directly. There was a study by Redmond and others in which cerebrospinal fluid changes in the concentrations of neurotransmitter metabolites could be examined in relation to the way certain behaviors change. To do that you have to have specific measures of affect and behavior for example, anxiety, anger, hostility and measures of motor behavior; you couldn't just measure the severity of symptoms of depression. You have to develop measures of these behavioral factors. Then we demonstrated, something few investigators have been able to show, a direct interaction between a change in the chemistry of the neurotransmitter metabolites and specific behaviors in the mental disorder. These results have been published in the *Archives of General Psychiatry* and in *Neuropsychopharmacology*. That is work I am very proud of. It is something that was always in the back of my mind when we were working on the collaborative studies. As far as carrying it over, we've written a few articles on important aspects of the process of behavior change affected by drugs. That was only possible because of our capacity to measure specific behavioral facets of the disorder. As a strong example of how these measures assist

understanding of how the antidepressants work, we asked what the first actions of these drugs are on the depressed patient. Is it, as most believe, to reduce depression as a whole or is it to reduce two major aspects of the disorder, anger and anxiety. Those who are deep into this field know that the serotonin system is associated mainly with impulsive aggression and anxiety. It makes sense that these drugs, if they are affecting serotonin level, should be impacting anxiety and anger and you would not be surprised that is what they do first, before they affect other behaviors and moods. A selective noradrenergic agent, like desipramine, also impacts anxiety, but it first activates "arousal", a motor function, so retardation is reduced. Should we not expect that a selective norepinephrine agent would relate to motor activity, arousal, when we examine studies of its association to these behaviors in the basic literature? So why have we not completed the story about how these drugs operate therapeutically in patients? We have tried in certain ways but for some extraneous reasons, it doesn't seem to take. There has been little examination for years, of the series of behavioral events that happen in the first week when you give these drugs. Clinical trials appear to dictate that the investigators only want to know what happened in four weeks or six weeks since that tells you whether the drug is effective as a treatment. If you ask where the intensity of my effort has been over the last few years, it's been on studying the interaction of chemistry and behavior that underlies how drugs work. Until we lay out that fabric and understand it we are not going to develop any better drugs. As long as we adhere to the mechanical clinical trial method for information on how drugs achieve their therapeutic effects, we are not going to learn anything new. Sorry to say that, but I think it's basically accurate.

SK: You came in at the beginning and created the basis for the field of psychopharmacology from the federal perspective of funding and stimulating people to ask the right questions.

MK: I helped.

SK: You have to pat yourself on the back for creating a tremendous field of study to understand and treat mental disorder.

MK: It has to do with hanging around long enough. You can actually get something done!

SK: Now you have to hang around a little further to finish it off.

MK: That's a good idea

SK: If you had the strings to pull to open up additional areas, what do you think the most important thing to do is? Can you speculate?

MK: I have written an editorial recently in the *Journal of Clinical Psychopharmacology* on the need to dispel some of the assumptions that underlie current clinical trials. I think it was Jules Angst, the great European psychiatrist, who called them "myths" in the field that continuously form or control the basis of what we do. For example, this notion that an antidepressant takes several weeks or months to act is one of the myths. It is an assumption that has been invalidated by many studies, by three recent meta-analyses, by independent studies and by editorials from investigators in other countries. It's time to let this delayed onset notion go, and to accept the evidence that antidepressant effects start to happen in a week, and that the main reason there is controversy and confusion is that investigators confuse recovery, with improvement in certain aspects of the disorder which represent specific early actions the drug. If we were studying actions on behavior we wouldn't be talking about full clinical response. You would want to know exactly what happens to behavior immediately, because effects on the neurotransmitter systems have been shown to be immediate. Where did the idea that nothing happens for several weeks come from? It is based on studies which were very influential in the early 1980's and despite those studies having significant shortcomings the results are in every textbook. Since few have examined drug effects on behavioral facets of the disorder during the first two weeks, the field has been late to uncover that actions on behavior and improvement, begin in the first week.

SK: So, you think this is more of a definitional issue about what recovery or improvement mean?

MK: If you want to know how the drug actually works, something that even at this point in the development of the field is not clear, you have to examine the entire therapeutic process; that means you have got to look at the actions in detail, particularly during that first period. It is understood in neurochemistry that all elements of neurotransmitter action must be examined. They are examined at every step of the way. Why have clinical trials not examined drug actions in terms of elements of behavior? Why not compare patterns of change with other drugs? Another problem is assuming that all classes of antidepressants we have now are initially affecting the same symptoms. That's another of the myths in the field. No matter that the different drug classes have different neurochemical effects, they are assumed not to have differential effects on behavior. But the evidence shows that they do have different effects on behavior. We published results on this as other people have. There is an article we wrote about ten years ago based on our experience with the collaborative study that I believe should have more of an impact on current thinking in this area. One conclusion that Jim Maas, the chairman, and I came up with was that the DSM system has become an impediment and could be a misleading influence on the design of future

research. If we don't transfer reliance on that diagnostic system to changes in behavior, mood and cognitive functioning we will never learn the nature of the elemental interactions between chemistry and behavior that determine what is going on in the therapeutic process. So, it is necessary to place less reliance on the diagnostic system in the design of clinical and drug studies and turn to the components of the disorder.

SK: Thank you for all this valuable information. Do you have any concluding comments?

MK: I am troubled by the faddish qualities that enter this field from time to time, that take us away from attaining closure on issues I have talked about. The current interest in genetics, for example, is well founded and it is surely going to be an important area in the future for all of our research. However, we have not yet resolved critical issues in the underlying chemistry and behavior and should continue that pursuit to achieve closure on understanding the basic mechanisms of action of these drugs.

On another subject, I would like to see us getting back to examining the effects of psychedelic agents; they offered so much promise not only in terms of generating new classes of drugs, but in opening up the still mysterious processes of the mind to scientific study. They had such unusual effects on memory, perception and learning, but we have no way of knowing what they might tell us about the mind, its potential and its limits, if we don't pursue further work in that area.

SK: Terrific! Thank you, Marty. It has been a lot of fun listening to your life experiences.

MK: Well, I appreciate your interest Steve. You gave me the opportunity to say everything I wanted to.

SK: Good, great, thank you

MARTIN M. KATZ

Interviewed by Thomas A. Ban

Boca Raton, Florida, December 12, 2007

TB: This will be a special interview with Dr. Martin Katz for the International Archives of Neuropsychopharmacology of the American College of Neuropsychopharmacology, about the birth of the College and about the role of the National Institute of Mental Health (NIMH) in the founding of the ACNP. We are at the Boca Raton Resort Hotel in Boca Raton. It is December 12, 2007. I am Thomas Ban. So, Marty, could you tell us about some of the background to the founding of ACNP.

MK: Thank you, Tom. Tom and I go back many years and lately we reminisce about at annual meetings of the College, how ACNP started. I am happy to be able to talk about some of the events that led to the founding of the college.

TB: Could you tell us briefly first how you got involved in psychopharmacology?

MK: As a young psychologist, I was doing research on the evaluation of psychotherapy and in other clinical areas in psychology and psychiatry. It was a very exciting opportunity for me in 1957 to come to work at the National Institutes of Health (NIH) to help to begin the Psychopharmacology Program. It was made possible for me by Jonathan Cole, who at the time, was the newly appointed head of that program.

TB: Could you say something about how this program came about?

MK: The establishment of a Psychopharmacology Program at NIH was the outcome of testimonies at the Congress from many psychiatric experts and lay professionals about the importance of the discoveries of some new psychotropic drugs in the mid-1950s. Introduction of these new drugs was by any stretch of the imagination a revolution in psychiatric treatment. These testimonials played a role in convincing the Congress of the United States of the need for a great deal of support from the Federal Government, to fund and to engineer the founding of a new discipline, neuropsychopharmacology, that could have a very great effect on the treatment of mental disorders in this country and in the world. One of the people who testified before the Congress was Nathan Kline, a young psychiatrist at the time.

TB: Could you tell us something about Nate Kline?

MK: Kline played a role in introducing reserpine, one of the first "tranquilizers", that was used in those days in treatment. He had a flamboyant presence, a very convincing manner and was very adept at influencing US Congressmen and other people. He deserves a lot of credit for getting that first two million dollars from Congress dedicated to the NIH to begin this new program in Psychopharmacology. At the National Institute, there was another formidable figure and that was Seymour Kety. He was in charge of the intramural laboratory program there. And, Nathan Kline and Seymour Kety were two of the members of the first National Advisory Committee on Psychopharmacology for the NIH. Their job was to make recommendations how to spend two million dollars, which at the time was a very large amount of money, to initiate research in this new discipline and to carry out certain projects and especially a very large collaborative controlled study, involving a large, representative sample of patients, on the effects of phenothiazine tranquilizers on schizophrenia. Most of the work done up to that point with these drugs had been done in smaller, "open" studies which were neither controlled or "double-blind".

TB: Who else were on the Advisory Committee?

MK: Others on this advisory committee were figures like Heinz Lehmann, the psychiatrist who introduced chlorpromazine, the first phenothiazine tranquilizer in the treatment of schizophrenia, in North America. Drs. Kline and Lehmann represented psychiatry on this committee. The Committee had to also include representatives of all the other disciplines, which were to make up this new field. That meant bringing together experts from the psychological, biological and psychiatric elements of the field. So, we had scientists like Lou Goodman, who had written the principal pharmacology textbook in the medical field, and Louis Lasagna, a very creative pharmacologist, who was at that time at the University of Rochester in New York. And, then, we had Howard Hunt and later, Gardner Lindsey, who were leading figures in the psychological field. We also had experts in the fields of statistics and epidemiology. The most formidable in the latter group was, I thought, Sam Greenhouse, who brought expertise in both statistics and in the clinical trials field. He was particularly critical in the development of the collaborative program, as were Mort Kramer, who ran a major epidemiologic facet of the NIMH), and some other figures.

TB: Who was the chairman of the Committee?

MK: The Chairman of the Advisory Committee was Ralph Gerard, a world-renowned neurophysiologist. You can imagine the difficulties that they had in weaving psychology, psychiatry and pharmacology together to create this new discipline. And, I, a young investigator, was given the task as the first Executive Secretary of this group, to observe and record the major points of their discussion and the nature of activities that were going on in the new field. My eyes, of course, were very big at that time. The people on the Committee were very impressive. And the battles that went on in the committee were provocative and highly productive. It would be worth documenting them in more detail. Just to give you an impression, Nathan Kline, credited with influencing the Congress to appropriate the funds to get this field started, as I mentioned, was a rather expansive representative of the field, and he was not very well liked by Seymour Kety, a basic scientist. Kety thought that Nathan Kline had exaggerated, overestimated what the new drugs could do and oversold the field to Congress. He wasn't too happy with the outcome and Congress' action. Everyone realized that if you did not present the case for expanding research on the new drugs in a salesman-like persuasive manner that the two million dollars would never have come in the direction of the Institute. So, those of us working in the program at that time, were not unhappy and weren't too critical of Dr. Kline. But, Dr. Kety had very sturdy principles in this respect and he and Dr. Kline were continuously arguing about the ethics and the direction the new program should take. I once labeled this the Battle of Saint Seymour and Nathan Kline, or something to that effect. Dr. Kety wanted most of this money to go towards basic research to provide the foundation in chemistry, pharmacology and biology for the new field, whereas Dr. Kline and Dr. Lehmann were for using a major part of the funds to carry out a very elaborate collaborative study, which would involve nine hospitals across the country with many clinicians and many patients to demonstrate the effectiveness of the new drugs. Their idea was that if the sample is large and representative enough, then the results of the study could be generalized to schizophrenic patients at large across this country and other countries, and consequently the demonstration of the effectiveness of the new drugs would move the field ahead. So, the Battle was basic science versus clinical science. But, the mission was clear in the Congress' recommendation, and we had a charge to carry out a collaborative study.

TB: How did Jonathan Cole get into the picture?

MK: Jonathan Cole, an extremely innovative psychiatrist and leader of the NIH psychopharmacology program, brought the research plan for the study to the Committee, and the Committee approved the funds to do the research he proposed.

TB: It seems that the Advisory Committee had a major role in starting the new field.

MK: The Advisory Committee, consisting of ten to twelve members, established the structure for the field of Psychopharmacology. Soon after this cross-national clinical studies program at NIH got started in 1960, the investigators began to act on the need for a national association, a scientific college.

TB: Could you elaborate on this?

MK: Because there were so many disciplines involved, it was a problem how to get the different disciplines to communicate with each other in order to solve the scientific problems unique to this new science. It required that researchers involved cross biological, psychological, psychiatric considerations in their research. It was in the course of this process that the concept of the American College of Neuropsychopharmacology evolved.

TB: Could you name some of the people involved in the creation of ACNP?

MK: The early creators of the college were people like Paul Hoch, Jonathan Cole, Joel Elkes, Ted Rothman, Dick Wittenborn. Elkes was a leading figure in the field; he had created the first Department of Experimental Psychiatry in the world in Birmingham, in the United Kingdom by setting up a model for merging science and psychiatry. He was also one of the most eloquent spokesmen in the field, emphasizing the importance of linking basic and clinical research. into the future. He had a major influence on my work as a young investigator because of his emphasis on the importance of creating a new clinical methodology in order to move the science forward.

TB: When was the College actually founded?

MK: In 1961.

TB: Were the annual meetings at the center of the activities of the new College?

MK: Yes. The first secretary/treasurer of the group was Ted Rothman. Then, it selected Dick Wittenborn, a scholar in psychology from Rutgers University with a long history of developing psychiatric rating instruments. He also had a flare for doing things well when it came to organizing conferences. Wittenborn established the home base for the annual meetings in Puerto Rico and set the annual meeting dates for the beginning of December. This location and date became a tradition that was maintained up to a few years ago. When the group was small it worked beautifully well. We would meet for a week. There would be some formal presentations, but half-

, or full day "Study Groups" were the main features of the meetings. They covered a range of topics from the Neurochemistry of Mental Disorders to Transcultural Psychopharmacology. The idea was that we had to move the field of clinical science forward as we couldn't wait for things to simply move on at their own rhythm as they apparently do move in the basic sciences. The study groups were heavily invested in attacking problems. We also had a wonderful study group on "Drugs in the Year Two Thousand" that was later published as an ACNP volume. We tried to look ahead into the future what would the field of psychopharmacology look like in the year two thousand from the knowledge base of in 1970. If you are Westerners and not from the Far East where cultural representatives plan in ten and twenty-year cycles, you are not likely to be looking more than a few years ahead. Most of us felt personally that we would not see the year two thousand. In that particular study group, we had celebrated people, like the novelist, Arthur Koestler, as one of the panelists, along with the anthropologist, Ashley Montague, and clinical scientists. And, when we look at the College's 2008 annual meeting program, we now see a different picture, a very different set of topics and a contrasting approach.

TB: So, you think that the meetings have changed and we have lost something with the change?

MK: I would like to see some of the spirit of the "study group" orientation from the early years in today's program. It helped distinguish the College from other scientific associations. We might have lost that, because the College has become big and the emphasis has shifted from the clinical to the basic science world. However, some of the clinical issues have remained unresolved. I would say that many of the problems of how we bring together disciplines like neurochemistry, behavior and pharmacology have remained unresolved and bedevil efforts to solve major problems like for example the "neurobehavioral" mechanisms underlying the effectiveness of the antidepressant drugs. I can, if I were to speak from a scientific basis, say that we still have not created those components that cross biological and behavioral spheres, a process that is necessary in order to understand how the drugs work. I don't think we should be leaving that area of research as quickly as we appear to be doing.

TB: So, you think we should continue with the old type of study groups?

MK: Yes. It would be useful to invite outsiders, leading figures from other fields to help extend our perspectives. We should also have plenary symposia that we had for example in 1973 in which I was proud to have David McClelland, the chair of psychology at Harvard, Eric Stromgren, from Denmark, one of the leading world psychiatrists on the epidemiology of schizophrenia, Sol Snyder,

one of the then rising investigators in the field of biochemistry and pharmacology, and the Nobel Laureate Linus Pauling. They stirred up our membership, especially Pauling with his ideas about the rigidity of scientific thinking, as he put it, the resistance to and the subsequent, unnecessary delay in the acceptance of new scientific evidence. I think those kinds of symposia could be put together again, to maintain the uniqueness of the organization and to stir us up again, to get us moving in the right direction.

TB: On this note, we should conclude this interview with Marty Katz. Thank you, Marty, for sharing with us this information.

MK: And, thank you, Tom. Thanks for having me

ON MARTIN M. KATZ

INTRODUCTION

Biographic information on Marty Katz was presented by Barry Blackwell (2011 a, b) in his Dramatis Personae to volume 4 and Introduction to Volume 9 of An Oral History of Neuropsychopharmacology. In his Preface to volume, Thomas Ban (2011 a) summed up Katz's essential contributions to the field of neuropsychopharmacology.

The information in this section was extracted from the respective volumes.

References:

Blackwell B. Dramatis Personae. In Ban TA, editor. An Oral History of Neuropsychopharmacology. Volume 4 (editor, Jerome Levine). Brentwood: American College of Neuropsychopharmacology; 2011a, p. XXII – XCV.

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Ban TA. Preface. In Ban TA, editor. An Oral History of Neuropsychopharmacology. Volume 4 (editor, Jerome Levine). Brentwood: American College of Neuropsychopharmacology; 2011a, p. IX – XXIX.

Biographic Information by Barry Blackwell

Martin M. Katz, born in 1927, was a mature young scientist with an undergraduate degree in chemistry and a doctoral degree in psychology from the University of Texas (1955) when psychopharmacology was at ground zero. In this interview (1995) by his peer, Jean Endicott, we obtain a unique "bird's eye" view of the evolution of our discipline that includes an inventory of its triumphs and tribulations over half a century later.

After two serendipitous meetings with Jonathan Cole Marty was recruited to become Executive Secretary of the first Psychopharmacology Advisory Committee at the NIH in support

of the Psychopharmacology Research Center (PSC), funded by Congress to develop the new field. This was a multidisciplinary body, chaired by a neurophysiologist and included pioneers who were psychologists, pharmacologists, biologists and psychiatric clinical researchers.

Dr. Katz began by reviewing and supporting novel research programs and after two years reverted to an active research role developing the eponymous Katz Adjustment Scales for measuring clinical and social adjustment and, in 1965, helping to organize the first large national conference on the Classification of Mental Disorders. This led later to co-editing the book, *"The Role and Methodology of Classification in Psychiatry and Psychopathology"* (1968). The following year he co-authored, *"The First Year Out; Mental Patients in Transition"* (1969), an early account of deinstitutionalization.

Over the next five years (1963-1968) Marty developed a laboratory at NIMH to study what he calls the "bad" psychedelic drugs; a class of compounds he feels was prematurely shelved for political reasons and which might be productively resurrected. During this time, he developed an interest in the influence of culture on the clinical manifestations of schizophrenia and wrote a book on the topic, *"Characterizing the Differences in Psychopathology among Japanese, Filipino, and Hawaiian Schizophrenics"* (1966). In 1968, he pursued this interest at the University of Hawaii before he was invited back to Washington to become Director of the new Clinical Research Branch at the NIMH. Its mission was to stimulate the field with conferences and by supporting collaborative research in five areas, depression, schizophrenia, psychosocial treatments, psychopathology and biological factors in mental illness. Over a 10-year span (1968-1978) the budget to accomplish this quintupled from $5 to $25 million.

Early on, a key event was the Williamsburg Conference (1969), which highlighted the neurochemical theories of etiology in depression and identified the key areas for development; better diagnosis and nosology, the genetic basis for disorders and ways of testing biochemical hypotheses. The conference and subsequent developments led to two books co-edited by Dr. Katz, *"Recent Developments in the Psychobiology of Depressive Illness"* (1972) and, *"The Psychology of Depression: Contemporary Theory and Research"* (1974).

One outcome of the collaborative approach that evolved during Marty's tenure was a seedbed for training a cadre of early outstanding researchers named in the interview. He attributes much of that success to two outstanding leaders, Gerry Klerman in the clinical arena and Jim Maas for the biological effort. A third leg to the collaborative ideal was the Clinical Research Center

concept which provided sufficient sustained support to develop programs and scientists. At the conclusion of his tenure as Director of Clinical Research Marty received the Administrator's Award for Meritorious Service from ADAMHA (1979).

After leaving the NIMH and leading up to this interview (1984- 2004), Dr. Katz held a number of appointments at Albert Einstein College of Medicine and Montefiore Medical Center including Director of Clinical and Experimental Psychopathology (1986-1993) and Professor and the first Chief of the Division of Psychology in the Department of Psychiatry (1984-1994). During this time, he was the Principal Investigator for NIMH funded research on the Psychobiology of Depression and co-edited two further books, *"The Measurement of Depression"* (1987) and *"Contemporary Approaches to Psychological Assessment"* (1989). At the time of the interview he was clinical Professor in the Department of Psychiatry.

Currently (2004-) Dr. Katz is Adjunct Professor of Psychiatry at the University of Texas Health Sciences Center in San Antonio. He now has a lifetime body of work that includes over 120 scientific articles and book chapters. Among his latest innovative work is the Video Behavior Evaluation Scales (VIBES). For almost thirty years (1970-1998) Marty served as a Consultant and Advisor to the World Health Organization on a variety of subjects and for ten years (1980-1990) he was Co-Director of the WHO Field Research Center in Hawaii.

Towards the end of this interview, with hindsight, Marty identifies three areas where the exciting discoveries of the first twenty-five years (1955-1980) were expected to fulfill hopes for the next quarter century (1980-2005). The first was that new "breakthrough" drugs would no longer be discovered by serendipity or accident but by designing new molecules faster and more effectively, based on biochemical knowledge. But since the introduction of fluoxetine in the early 1980's "nothing really remarkable" has appeared.

Secondly, that the biological basis of psychiatric disorders would be revealed; a simple blood test at the first interview would provide the diagnosis. This too has been a disappointment, "we have yet to find a biological marker for any mental disorder."

Thirdly, that the mechanism underlying the action of drugs would be known, but "that too, is still clouded."

Late in the interview Dr. Katz tries hard to uncover a contemporary silver lining; instead he identifies a shortcoming that may account for the lack of progress. He wonders if our excitement

with molecular biology and neuroimaging has led to the neglect of a better understanding of behavior. “If we go to the trouble to get down to such refined, intricate biological measurements, we should be doing the same kind of thing in the sphere of behavior.”

The fact that this interview was conducted fifteen years ago hardly modifies its contemporary relevance. Its insights are from a man who was there from the very beginning, a member of the ACNP from 1963, Council Member (1972-1974), Vice president (1978) and now Life Fellow Emeritus. Dr. Katz is also the editor of Volume 10 in this series, devoted to the history of the Organization.

Additional Biographic Information by Barry Blackwell

In 1965 *Martin M Katz* was among the first in the United States to address the methodology of classifying psychiatric diseases. In 1969, he published findings on the influence of symptom perception, past experience and ethnic background on diagnostic decisions. By the end of the 1970s, the focus of Katz’s research shifted to the psychobiology of depression. In 1987 his team was first to challenge pharmacological findings that indicate a two to three-week time-lag between initiation of treatment and antidepressant effects. Subsequently, in 1994, they published findings on the relationship between drug induced actions on neurotransmitter systems and changes in the behavior and emotions of depressed patients, in 2004, on the onset and early behavioral effects of pharmacologically different antidepressants, and in 2010, on “links” between neural and behavioral changes in the course of treatment of depression with antidepressants.

Essential Contributions by Thomas A. Ban

Martin M Katz, one of the first members of Jonatan Cole’s team at the Psychopharmacology Service Center of the National Institute of Mental Health, introduced the Katz Adjustment Scales in 1963 for measuring adjustment of social behavior in the community of patients discharged from hospital after successful pharmacological treatment. He also developed a “video methodology” for research in psychopathology and psychopharmacology in the 1970s. In an NIMH sponsored multi-center clinical investigation in depression, Katz and his associates demonstrated clinical changes within a week of commencement of treatment with SSRIs and TCAs and challenged the theory about delayed onset of anti-depressant effects. The changes with paroxetine within the first week were in anxiety and hostility whereas the changes with desipramine were in retardation and depression.

Introduction

An Oral History of Neuropsychopharmacology is a 10-volume series published, in 2011 by the American College of Neuropsychopharmacology. It is based on interviews with neuropharmacologists and psychopharmacologists of the first generation, most of them conducted at the annual meeting of the College. The interviews were organized into a 10-volume series and edited by Thomas A. Ban with an editors' team each responsible for the editing of one (or two) volumes. Marty Katz was a member of this team, responsible for editing volume 10, History of the ACNP. His Introduction (Katz, 2011c) to volume 10 was adopted here.

Reference:

Katz MM. Introduction. In: Ban TA, editor. An Oral History of Neuropsychopharmacology. Volume 10 (editor, Martin M. Katz). Brentwood: American College of Neuropsychopharmacology; 2011c, p. XXVI-XXXIV.

Introduction to Volume 10

This volume explores the history of the ACNP beginning with its founding in 1961. The narrative is divided into two parts. Part 1 consists of transcripts of specially prepared interviews for the 50th anniversary of the College with three of the key Founders of the College and with two very close observers of its history. In addition, one transcript provides a perspective, in a group interview with foreign corresponding members, on the impact of the College, internationally. Part 2 is based on excerpts tracts from the interviews presented in this series. The founding of the College is described in the excerpts from the Founders and the chronicling of events that defined the College over the succeeding 50 years is described through excerpts from the comments of the Presidents, chronologically ordered. Then, the critical issue of the "mission" of the College, as originally formulated by the founders, and how it has evolved over this period, is elaborated. To sharpen the nature of the views expressed on this issue for the reader, the excerpts are separated into those expressed by the basic and transdisciplinary scientists and those reflecting the views of the College's mission by the clinicians and clinical scientists. The reader will learn that the

mission, as part of the story of the College, will continue to unfold, and is by no means, completely resolved.

The excerpts in Part 2 relating to the overall mission of the ACNP bring us from the early days of the College in 1961 to the present scene in the history of neuropsychopharmacology. The early organizers were quite clear on what they wished to accomplish in founding this new unique scientific institution. The founding group consisted, in great part, of the psychiatrists who had witnessed the impact of this revolution in treatment on their discipline and on their patients. These were the "treaters", key figures such as Frank Ayd, Heinz Lehmann and Nathan Kline, the administrators of large clinical organizations, such as Paul Hoch and Henry Brill, and the clinical scientists in positions of governmental authority, e.g., Jonathon Cole. The neuroscience "transdisciplinarians," Joel Elkes, Bernard Brodie and Seymour Kety, envisioned a new science in psychiatry and psychobiology.

The field's first challenge was to make the remarkable advances of the 1950s in treatment by making drugs credible to the clinicians, and encouraging their use. The main task was, however, to frame the problems of the new science in a way that would bring scientists from several disciplines, pharmacology, neurochemistry, psychology together with clinical practitioners.

The key figures were aware that the disciplines represented different "cultures," that their representatives employed different languages, and arrived with different backgrounds of experience and training. The central issue facing this small group of professionals constructing this new College's framework was creating a language that was understandable to all the disciplines to facilitate the interaction and identify critical problems.

In Part 1 of this volume, interviews with several of the founders, Jonathan Cole, Frank Ayd, and Joel Elkes, a leading figure of the psychiatric establishment, Thomas Detre, and myself, are presented. I was at that time, Executive Secretary of the first National Institutes of Health Advisory Committee on Psychopharmacology. The interviews in Part 1 express the hopes of the founding group for the future role of the College in development of the science and in advancing the clinical impact of neuropsychopharmacology. In addition, there is a recorded group interview in Part 1, conducted by Alan Frazer, current (2011) secretary of the College with leading psychopharmacologists from other countries, commenting on the impact of the College internationally.

The College is 50 years old this year and this is probably an excellent point in time in the historical development of neuropsychopharmacology to consider whether the College is progressing in directions that are productive and as satisfying as they were when it was first established. To meet this goal, I have screened the more than 200 interviews of ACNP members to select comments that speak directly to their experience with the College and separated the comments of the Founders from the comments of the Past Presidents and the comments of the rest of the membership. I also separated, as indicated before, the comments which deal with the College's mission.

Certain aspects of the overall concept of the College held by the founding members have not changed over five decades. The originators viewed the College as a place to bring together scientists and clinicians from the academic and clinical worlds, from the laboratories and hospitals, who would represent the broad range of disciplines that were engaged in developing the new field of neuropsychopharmacology. The new drugs created a revolution in the treatment of the severe mental disorders. It would, therefore, have a major impact on the ways in which psychiatrists would be trained. Thus, it would require modifications in the academic setting, and in the management of clinics and hospitals. It would require changes in emphasis in training in regard to the various disciplines that participate in the scientific education of psychiatrists, changes, e.g., in the roles of neurochemistry, pharmacology

The College brought to the fore new issues and problems that clinicians and scientists would have to confront, such as the reliability of the then current psychiatric diagnostic system, the effective utilization of the new drugs, their applicability and dosage specifications in the treatment of specific classes of disorders. And at the basic science level, questions arose about then unknown neurobehavioral mechanisms underlying the efficacy of these drugs, how to develop more effective drugs with fewer side effects and ones applicable to still untreatable conditions. To deal with such problems the College would have to assemble, in addition to the working clinicians, scientists representing various disciplines.

The History

In his Part One interview Jonathon Cole provides a narrative on the founding of the College, the primary players, its original composition and its goals. Further details are provided by Frank Ayd who describes the climate at the time, in the world of psychiatric practice. Tom Detre describes later, how the leaders in psychiatry would structure their University departments and educate the new psychiatrists, and how they would meld the new neurosciences and clinical practice. Joel Elkes, the founder of the first Department of Experimental Psychiatry, describes the scientific events that led to the creation of psychopharmacology as a discipline and its conception for linking brain function to behavior. Thus, he set the theoretical foundation for the establishment of the College.

Others outline the early makeup of the College, its aspirations to link basic and clinical science and the selection of the content and the structure for its early meetings. In that group, we find such early figures as Heinz Lehmann, Karl Rickels, William Turner, Tom Ban, Albert Kurland, Erminio Costa and Leo Hollister. So that a reading of the excerpts from the interviews in Part 2 of this Volume provides a relatively complete description of the early days citing the important figures in the several sciences who helped construct and establish the College.

The comments also bring out the cast of people who conceived the College and were instrumental in its establishment, but who have since passed away and were not available for interviews. Among them, most prominent were: Theodore Rothman, who was ironically, a psychoanalyst practicing in Los Angeles, Paul Hoch, the Commissioner of Mental Health in New York who was identified as the initial leader of the effort, Bernard Brodie, renowned for heading the NIH Laboratory where a number of distinguished figures began their studies, including Nobel laureates, Julian Axelrod and Arvid Carlsson, basic investigators, Erminio Costa and others who generated early work on the neurochemical mechanisms underlying drug effects. Later, in 1964, J. Richard Wittenborn, an academic and clinical methodologist in psychology, became the Executive Secretary of the new College.* Paul Hoch for reasons of protocol, rejected Puerto Rico as a meeting place. Hoch died, however, before the planning of the first annual meeting was completed and his successors thought better of that rejection and decided to hold the meeting in San Juan.

The quality of the group that founded the College, was of course, outstanding. The current members owe to this small group, the concept of crossing of the several sciences with clinical practice, setting high qualification standards for entering new members and designing the informal "study group" at the annual meetings. The "study group," with its attention to identifying critical problems that required input from more than one discipline, created the social and scientific atmosphere that would foster collegiality and communication.

Fortunately, much of what these dedicated pioneers had hoped would endure in the structure of the College and in the quality of the interchange, has in fact, stood the passage of time. But, as with all organizations, the advances in the sciences and how the membership evolves over the years, result in major changes in the scope of knowledge and consequently, in the nature of the organization itself. The organization becomes steadily larger, more difficult to structure in a manner satisfactory to all groups, and with the advances in knowledge and technology, more complex. Yet as the comments clearly display, the majority of members still view the College as unique in its capacity to bring together the brain scientists and the clinical practitioners. Due to the high quality of the meeting presentations and the congeniality of the setting, members continue to view the annual meeting as the "highlight of the year". The participants view their membership in the ACNP as by far, their most coveted affiliation.

Nevertheless, the changes in the science, the content of the programs and the composition of the membership have resulted in islands of discontent that seemed to have increased in magnitude over the years. These are most notable within the clinical science group. The burgeoning of neurosciences, the increase, as well as the importance of molecular biology and genetics have inspired the progress of science in this area. Yet these advances have not, in the eyes of many, been matched by developments in the clinical science of mental disorder, e.g., in further advances in the basic psychopathology of the disorders. This has resulted in an imbalance and a decline in the role of the clinical scientist. Consequently, there has been a decrease in the acceptance of clinicians into the College, and in the clinical content of the annual meeting program.

Leading senior figures in the College have spoken openly about this imbalance, pointing out that it was the clinical discoveries that ignited neuroscience and at its beginning, was the center of the College's concern. Ways to deal with this issue are adumbrated in the excerpts of John Davis, Max Fink, Fred Goodwin and Carl Salzman in Part 2.

The Founders' Mission and its Evolution During its 50 Years

In this section, we deal directly in the excerpts with the mission of the College and how it has evolved over several decades. The excerpts are from members who entered the College as early as the 1960s. These excerpts are intended to display how the mission was envisioned over the years by the various members and how the general concept of the College's mission managed to maintain itself over the decades. I start with quotes from Joel Elkes and Heinz Lehman, whose eloquence on issues like these is well known. We then move to current conceptions of the College. The reader can then consider what can be done about fixing current (2011) problems.

To fully understand how and why the College was established it is useful to read in their entirety, the interviews in this volume, of the several figures who were around at its birth. *Frank Ayd* representing the "practitioners," when introducing the revolutionary new treatments for the mental disorders to his peers felt: "*I think aside from looking at the drugs and being persistent, I was sort of a St. John the Baptist in the wilderness preaching the gospel of the psychopharmaceuticals and their potential value for peopl*e."

Joel Elkes, an academic, was one of the neuroscientists who provided the conceptual framework for the new science of psychopharmacology, and later, the theoretical foundation for the College.

Jonathon Cole, a scientist administrator and clinical investigator, established NIH's first grants program in psychopharmacology for support of basic and clinical science. He saw at the outset, the need to provide the resources for the early clinical investigators who uncovered the first drugs: *"…we'd been working with people who did early clinical drug studies and I decided they were going from little study to little study and they didn't have any enduring support and it would be a good idea to have some kind of grant program to carry them along and allow some things on their own that were not drug company directed.*"

Later, through an NIH supported collaborative program, Cole led the conduct of the first definitive, randomized controlled study of the efficacy of the phenothiazines for acute schizophrenia. He, thus, provided a model in the 1960s for the scientific evaluation of new treatments in psychiatry, a model that did not exist before the drugs entered the scene.

Thomas Detre, a University Department Chairman, entered the College somewhat later but helped to lead the way in altering the structure of University departments and their approach to educating psychiatrists. The academics must lead in this new era by providing the neuroscientific foundation for training in clinical practice. In his words: *"I felt time has come to establish a department of psychiatry which would first and foremost concentrate on translational and strictly clinical research to improve the management of the patients."*

This volume editor, *Martin Katz*, was the executive secretary of NIH's first Advisory Committee on Psychopharmacology and as a psychological investigator observed the beginnings of the College and the contributions of the multiple disciplines. He sketches the role of each faction in the College's organization: "*The NIH Advisory Committee made up of ten to twelve members, representing the several basic and clinical sciences, really established the backbone in a way for the field of psychopharmacology. Soon after this cross-national clinical drug study program got started, the investigators began to act on the need for a national association, a scientific college.*"

Finally, we consider what has changed in the mission, structure or content of its annual program and the composition of its membership. Have the changes been good or have they worked against the early aims and accomplishments of the College? Have they fostered, facilitated progress in the sciences and the creation of drugs or have they retarded, blocked progress? If the latter, what future changes should be considered to retrieve, fortify the central goals of the College.

The members confronted the immediate, early issue of why, as Leo Hollister put it, was it necessary to establish another scientific society. The group had to define the new discipline and indicate how it was distinguished from the several scientific and professional societies that apparently, covered the same territory. In so doing they defined its mission, its conceptual base, the mix of sciences and clinical practice that would be represented in its membership. The design of the annual meetings was dedicated to dealing with unique problems created by the new drugs and to encourage communication across disciplinary lines. On the rise of the new sciences, no one defined the mission of the College more eloquently than Joel Elkes: "…*there was a lot of fluidity and mobility in the field, and crossing over into disciplines there was an emerging understanding that there are four footings of the new discipline: neurochemistry, which was maturing so to speak because we did not have anything more in neurochemistry than written in Thudichum, electrophysiology, animal behavior and clinical trials. These were the four footings, which I saw as essential elements of any psychopharmacological enterprise worth its name."* And, then, Elkes

continues: "*For example, the whole question of communication in the nervous system cries out for collaboration between neurophysiologists and psychologists, education experts, communication engineers, language-translation specialists and so on. And they don't know what we know! And we don't know what they know! And the knowledge has to come together by work at the bench and common new languages will evolve as we work together. So, we need alliances and alliances, even with strange fields; to be trans-disciplinarians; make it evident that this is a science like no other is, it has special characteristics of its own and will in time have earmarks by which it is known. It is not only molecular biology; it is not only electrophysiology; it is not only animal behavior; it is not only clinical syndromes. It is the conversation and the interaction between these areas, which matters and we must do all we can to enhance the conversation. This is what the College can do like no other organization nationally and internationally*."

How do you promote interdisciplinary dialogue? How do you solve problems and overcome obstacles to scientific discovery when the solutions require the interaction of scientists from different backgrounds of training and language, on the one side, and interpreters of the clinical phenomena that define the mental disorder, on the other? Here again, Elkes defines the function of the innovative sessions he introduced at the annual meeting, the "study groups": **"***The idea was to select people from different disciplines into small groups and give them the opportunity to talk to each other. That's very simple and it developed very, very well. Study groups led to a sense of scholarship identity, of owning certain areas of psychopharmacology. And, it worked."*

The Core Issue of Maintaining Balance

The mission, the composition of the membership, the design of the program at the annual meeting and the central research and clinical problems on which the new organization was focused, have all changed, evolved over the decades. But the essence of the College hopefully, remains the same. The members in their interviews discuss all these issues and provide their own perspectives on how the College will fare in the future. Most notable, however, among the statements, most of which are laudatory concerning its evolution, is one change which a significant group of founders and early members deplore and believe have to be attended to soon in a positive way. That is the "decline in the role of clinical issues" generally in the College's overall conception and mission goals. Its effects are reflected, in the decrease in the selection of clinical scientists for membership, the increasing majority of basic scientists, the dominance of molecular biology and genetics in its

focus, as reflected in the apparent near monopoly of content in the annual meeting program, as well as in the contents of the College's Journal. This group includes John Davis, Max Fink, Jonathan Cole, Fred Goodwin, Walter Brown, Turan Itil and Carl Salzman.

The members recall that it was the discoveries by clinicians of the potency of the new drugs in patients that ignited this revolution in treatment, and served, if indirectly, to initiate a new area of neuroscience. The new society was then aimed at both facilitating the development of more effective drugs, and advancing neuroscience. This disquiet is most clearly expressed by John Davis: "*I think they (the early years) were very exciting. Since then the ACNP has changed tremendously and I don't think it's changed in the good direction. Back in the early days there were about a third of basic scientists, maybe a third were psychologists, and a third, psychiatrists. But some of the psychiatrists were involved also in basic science. There was pretty much of a mixture, clinicians may have been in the minority, but there were plenty of clinicians attending. Now it's changed; mostly basic scientists are attending. My feeling is that unless they make an effort to involve more clinicians, ACNP is going to change to a basic science organization.*" And from another vantage, Frederick Goodwin says: **"***I get uncomfortable when people say that basic science is the source of everything. In fact, much of what we understand about the synaptic connections of the central nervous system, as you know, came out of efforts to understand how imipramine worked. And it seems to me that it was the effort to understand psychoactive drugs that created functional neuroscience."* They see the failure to continually reinforce and expand the clinical side of this venture as, in part, responsible for the lag in the development of new classes of drugs. They are concerned as Leo Hollister expressed it that the College is fast **"***becoming a secondary society of (the large world of) neuroscience,"* rather than the truly multidisciplinary organization the Founders had envisioned. The critiques extend to the method of selecting new members, and to the design of the annual program. More time needs to be devoted to clinical issues, there has to be more use of the original "study group" concept and the Journal Editor has to be more active in soliciting clinical study papers for Neuropsychopharmacology.

By contrast, the basic scientists are more satisfied with the evolution of the College. They are more pleased with the advances in science and technology during the past five decades and are satisfied with the current balance. They view the evolution of a greater focus on molecular biology, neuroimaging and genetics as a natural direction for the field to follow and are less concerned about the lag in clinical science and the introduction of novel treatments.

Floyd Bloom analyzed the problem of "imbalance," however, as the consequence of the difficulties for clinicians "*in keeping up with the wave of new knowledge in the neurosciences and for the basic scientists, keeping up with the modifications of the classification and diagnostic systems for the mental disorders."* This interferes with achieving integration of basic and clinical scientific developments, or as he put it, with "*the cohesive element, which was the intermingling between basic scientists and clinical scientists*." In this volume, the excerpts of interviews of the group relevant to these concerns are recorded and can be read directly in the section that consists of "Mission Statements: Clinical Scientists."

Other Issues: Industry, the International Perspective

On the role of Industry in the affairs of the College and on its future, the members express a wide range of opinions. To some, Industry has been generally supportive of the College's overall aims in enhancing its annual program and in helping to fund important educational objectives. To others, its influence has not always been positive, as seen in Industry's tardiness to provide data from failed clinical trials of new compounds. In this respect, Industry has significantly impaired the trust that clinicians and investigators have in the results of clinical trials. George Simpson said "*that's true that the sponsorship of the trial seems to dictate what the results are going to be. I don't think people cheat, but I think you are unlikely to design a study that could possibly go against what you would like to see."* Those who work in the clinical trials field are also acutely aware that except for several drugs with minor variations in mechanisms from the established ones, no new classes of antidepressants have been introduced since the SSRIs in 1979. To rectify problems in this area, the College is urged to provide continued vigilance regarding the participation of the pharmaceutical Industry in its affairs, e.g., in planning its annual program. The College might want to encourage NIMH to enlarge its own role, i.e., to return to its place as the major financial source for testing new drugs, to encourage investigators to apply for NIMH grants in this area and to pursue, both within and without Industry, the development of new drugs for the entire range of mental and substance abuse disorders.

There are other concerns about the structure of the annual program. For the most part, however, the membership as a whole is quite pleased with the directions in which the College had progressed. They see a sound future as the science advances on the national and international scenes and as clinical practice increasingly improves. This optimism about the future and the

breadth of the College's impact is brought home in the interchange of the Foreign Corresponding Members led by Alan Frazer. The international members see the informal nature of the interactions at the College's annual meeting as very different from what they are accustomed to, as stimulating new ideas, new collaborative arrangements, and providing a model for their own European College. We can look forward, as Joseph Zohar points out, to the further development of *"personalized medicine"* based on advances in genetics. Then, according to Arvid Carlsson, the introduction of "*an entirely new diagnostic system,*" a paradigm shift, one created from the new knowledge of brain circuits and imaging technology, reminds us that "*drugs don't care about the boundaries between one diagnosis and another."*

The concerns that remain for the field are how to rebalance neuroscience and the clinical sphere, how to maintain the vitality of the organization, the vibrancy of its program and the stimulating, interdisciplinary dialogue, how can the College, a continuing "work in progress", be helped in reaching its goals in achieving effective treatments for all of the mental disorders and in making them available as rapidly as possible to the treating clinicians.

The excerpts from the interviews of the Founders and Members carry within them the historical picture of development over these past five decades and offer the planners of today (2011), a blueprint for future success in this critical area of the health sciences.

CONTRIBUTIONS TO INHN'S WEBSITE

INTRODUCTION

From the time of the launching of INHN's website in 2013 until he passed away in 2017, Marty Katz was a major contributor to INHN's website. Three of his essays (Component-Specific vs Diagnosis-Specific Clinical Trial in Depression; Multivantaged vs Conventional Assessment Method; and Onset of Clinical Action of Antidepressants) and two of his book reviews (Depression and Drugs the Neurobehavioral Structure of a Psychological Storm; and Clinical Trials with Antidepressants How Changing the Model Can Uncover More Effective Antidepressants), have triggered active exchange that lead to collated document which are being converted into a volume for distribution in our Educational Series to become accessible in our Educational Series In addition , he contributed 13 other postings: five posted in Dictionary, three in Books, two in each, Controversies and Perspective, and one in E–Books. These 13 postings with their original posting date indicated are included in this section.

DICTIONARY

Component Specific Clinical Trial

The term, "component-specific clinical trial" (CSCT), first appeared in a paper by Martin Katz, Charles Bowden and Alan Frazer, published in 2010. It was more completely defined three years later, in 2013 by Katz, as a trial in which the method for measuring outcome is profiling the specific drug effects on the principal behavioral, mood and cognitive components of a disorder instead of focusing exclusively on changes in the overall severity of that disorder. The CSCT was employed in a series of clinical trials in the study of drug effects in depression in the early years of the 21st century, the findings of which were reviewed in Katz's monograph, Depression and Drugs The Neurobehavioral Structure of a Psychological Storm, published in 2013.

Katz MM. Depression and Drugs The Neurobehavioral Structure of Psychological Storm/ Berlin: Springer; 2013, pp. 61-71.

Katz MM, Bowden CL, Frazer A. Rethinking depression and the actions of antidepressants: Uncovering the links between the neural and behavioral elements. J Affective Disorders 2010; 120: 16-23.

April 3, 2014

Multivantaged Assessment Method

The term "multivantaged assessment method" (MVAM) was introduced, in 1984 by Martin M. Katz and co-investigators in their report of the US National Institute of Mental Health (NIMH) Collaborative Study of the Psychobiology of Depression. It is based on a dimensional conceptualization of mental disorders, and the assumption that mental disorders are structured by interaction between their measurable emotional and behavioral components. Because of the many ways these components can be manifested, in a multivantaged assessment, methods of assessment from several "vantage" points are combined. The prototype multivantaged assessment includes quantified observational methods, such as ratings scales by experts, subjects' judgment on current state, and measurement of cognitive and psychomotor performances. The multivantaged assessment method was employed in a series of studies in depression, in the Departments of Psychiatry and Pharmacology in the University of Texas Health Science Center at San Antonio, by Katz and his associates, and the term reappeared in 2004, twenty years after its introduction, in a report of these studies on the "onset and sequence of clinical actions" of antidepressants, published in the International Journal of Neuropsychopharmacology. Information on the development and definition of the concept of MVAM was presented by Katz in 2013, in his monograph, Depression and Drugs. The Neurobehavioral Structure of a Psychological Storm.

Katz MM. Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm. New York; Springer: 2013, pp. 21-34.

Katz MM, Houston JP, Brannan S, Bowden CL, Berman N, Swann A, Frazer A. A multivantaged behavioral method for measuring onset and sequence of the clinical actions of antidepressants. International J of Neuropsychopharmacology 2004; 7: 471 – 9.

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May 1, 2014

National Advisory Committee on Psychopharmacology

The National Advisory Committee on Psychopharmacology was established in 1956 by the National Institutes of Health (NIH) to guide a new program of the National Institute of Mental Health (NIMH) that would stimulate research in the new science of psychopharmacology. The new program was implemented with the establishment of the Psychopharmacology Service Center (PSC) from the 2 million dollars allocated in 1956 by the US Congress to the NIH in response to the discovery of new drugs for the treatment of mental disorders. The Committee consisted of expert psychiatrists, pharmacologists, psychologists and statisticians. Its members included Louis Goodman (Pharmacology), Seymour Kety (Biological Science), Nathan Kline (Psychiatry), Morton Kramer (Biostatistics) and Joseph Zubin (Psychology). The appointed Chairman of the Committee was Ralph Gerard; the Executive Secretary, Martin Katz (Katz, 2011). The role of the Committee was to both guide the activities of the PSC, its leader, Jonathon Cole and staff, in implementing the program initiatives, and to review applications for research grants from outside investigators in the field (Cole, 2011). In the early 1960's, most of the Committee's research grant review function was transferred from the NIMH to the NIH. Its prime function, following the PSC becoming the Psychopharmacology Research Branch in 1965, was to advise on ongoing and planned clinical research goals of the psychopharmacology program.

Cole JO interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 10- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 45-53.

Katz MM interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 10- "History of the ACNP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 77-81.

November 6, 2014

National Institute of Mental Halt Collaborative Study in Psychopharmacology

The National Institute of Mental Health Collaborative Study refers to the study the Psychopharmacology Service Center (PSC) of the National Institute of Mental Health (NIMH) was charged with to carry out under the guidance of the National Advisory Committee on Psychopharmacology (Katz 2011). It was a nationwide controlled study of phenothiazine treatment in acute schizophrenia that was led by principal investigators Jonathon O. Cole, Gerald L. Klerman and Salomon Goldberg and carried out in disparate public, private and university hospitals (National Institute of Mental Health, Psychopharmacology Service Center Collaborative Study Group 1964; National Institute of Mental Health, Psychopharmacology Research Branch Collaborative Study Group 1967).

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National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment of acute schizophrenia: Effectiveness. Arch G Psychiat 1964; 10: 246- 261.

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October 16, 2014

Psychopharmacology Service Center

The Psychopharmacology Service Center (PSC) was a program of the National Institute of Mental Health (NIMH). It was created by the National Institutes of Health (NIH) from the 2 million dollars appropriated by the US Congress in 1956 to initiate a grants program and national effort to stimulate research and treatment in the application of new psychotropic drugs. Jonathon Cole, a young psychiatrist, was appointed to lead the Center with the guidance of a National Advisory Committee, chaired by Ralph Gerard (Cole 2011; Katz 2011). The Center initiated a basic research grants program, conducted a nationwide Collaborative Project to evaluate the new drugs *(NIMH Collaborative Studies in Psychopharmacology*), created the *Early Clinical Drug Evaluation Unit (ECDEU)* network to develop new drugs, and published a new periodical, the *Psychopharmacology Bulletin.* The name of the Center was changed in 1965 and established at the NIMH as the Psychopharmacology Research Branch.

Cole JO interviewed by Ban TA in *An Oral History of Neuropsychopharmacology - The First Fifty Years: Peer Interviews* (Thomas A. Ban, editor), Volume 12- "History of the CINP" (Martin M. Katz, volume editor). Nashville: American College of Neuropsychopharmacology; 2011. p. 45-53.

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October 30, 2014

CONTROVERSIES

The Need and Rationale for Shortening the Clinical Trial for Antidepressants

The major characteristics of the current model for the clinical trials of new, putative antidepressants (ADs) has not been modified in any substantive manner, since its establishment some five decades earlier. This is despite the fact that the conception of the depressive disorder has been subject to change over the years, a great deal has been learned about the timing and mechanisms of action underlying the efficacy of the ADs, and the most prevalent forms of the disorder presented for treatment today in the outpatient clinic, are probably not as severe as those on whom the original model was targeted. The current model due in great part, to its reduced sensitivity to clinical change when applied to less severely ill patients, resulted in many failures to identify potentially useful drugs. In addition, the sampling and methodologic procedures for a trial are known to be excessively expensive for the pharmaceutical companies, resulting in a declining interest in this sphere of activity and complete abandonment of CNS drug development by several major companies. In many ways, it can be shown that applying the established trial as a routine procedure is in fact, a very wasteful use of resources. There is in other words ample evidence of both a scientific and a practical nature to reexamine the established model and to strongly consider major modifications in the trial procedures.

I have in previous papers (Katz, 1998, 2008; Katz et al., 2006) acknowledged with others the existence of certain statistical issues and the limitations of the Hamilton Depression Scale (1960), the sole method of evaluation in the established model. There have over time, however,

been significant improvements in procedures. For example, Bech (2011) and Rush et al. (1986) have contributed to increasing the sensitivity of the Hamilton method and Montgomery and Asberg (1979) have sharpened the focus on measuring change, all by introducing new methods of evaluation. They identified the major source of the problem in the methodology of evaluation. In my own work, I further extended the methodological approach by first setting aside the traditional diagnosis and adopting the more precisely descriptive dimensional concept of the depressive disorders. I then developed a set of evaluative methods that measure its major components and dimensions. This revision of methodology, thus provides a way of refining the characterization of the illness and makes possible the profiling of the diverse and multiple behavioral effects of the drugs.

My approach is designed to capture both the changes in overall severity of the disorder, the primary aim of the clinical trial, and in the diverse critical behavioral components we have uncovered over the years. It is these components we have learned, that are more specifically targeted by the drugs, rather than the "disease" itself.

This focus on the profile of clinical drug actions contributes to greater sensitivity. Along with this more refined examination of drug actions it then makes it possible to detect very early changes in the clinical state, not detected by the established model. It was through this approach that it was first confirmed that clinical action of effective drugs begins within the first two weeks, contrary to the then textbook notion that clinical effects do not appear until several weeks of treatment (Katz et al., 1987). Since then there have been several large sample, multisite studies conducted that have established this early onset as fact (Stassen et al., 1993, 1997; Szegedi et al., 2009), and led to further studies, several of which have shown that 60 to 70% of the efficacious drug's total clinical effects will occur during those first two to three weeks.

When the clinical implications of these more recent findings are examined, we become aware that it may well be possible, that simply on the basis of the drug's clinical actions during those first two weeks, to predict whether the drug will be efficacious for the targeted disorder. If so, we could shorten the clinical trial, a modification that would result in major reductions in the excessive cost of the trial, and even more important, make it unnecessary to burden already distressed patients in controlled studies with several weeks of ineffective drug or placebo treatment.

On this particular issue of prediction, here is the evidence so far:

(1) There are a number of early studies that reported early clinical changes with the ADs and showed them to be predictive of later response to the drugs. They include studies of Coryell et al., 1982; Katz et al., 1987; 2004, Khan et al., 1989; Nagayama et al., 1991; Stassen et al., 1993; Boyer and Feighner, 1994; and Szegedi et al., 2003.

(2) More targeted research over the years has been conducted and reviewed by a number of groups. They have established that "among responders the onset of improvement with ADs occurs in more than 70% of cases within the first three weeks," later reinforced by Posternak & Zimmerman (2005) who reported that "60% of the improvement that occurred on active medication and placebo, took place during the 1st two weeks of treatment," and evidence summarized by Taylor et al. (2006) in their review who concluded that "one-third of the total effect of SSRIs after six weeks of treatment is seen in the first week." Of even more significance, it was quite clear from the Stassen et al. (1997) and Szegedi et al. (2009) multisite studies of upwards to thousands of patients that absence of clinical changes during the first two to three weeks of treatment with diverse ADs is associated with less than 10% of patients responding at outcome, i.e., almost certain non-response to the experimental treatment. For a more thorough review of background research on the issue see Katz (2013). There is, in other words, much evidence that the nature of the patient's response as early as two weeks, i.e., evidencing "improvement" or "no change," is highly predictive of a putative AD's efficacy, as measured at outcome of a 4-12-week treatment course

(3) Katz, Berman, Bowden and Frazer (2011, 2015) more recently attempted to evaluate the two-week prediction hypothesis in a relatively small size patient sample from the Katz et al. (2004) onset study. Viewing the attempt as a "proof-of-concept" effort, they were able to confirm that the two-week results were highly predictive of outcome and strongly support the conclusion that two weeks is sufficient time to judge whether it is necessary to proceed further with the clinical trial. That study's major limitation, as noted, was the relatively modest sized patient sample. That led to the recommendation that a prospective study including a large multisite diverse sample of patients diagnosed as major depressive disorder, be conducted, that would extend the test study findings. The results could lead to the acceptance of much improved, markedly less expensive models for clinical trials, such as those proposed in the test study.

The conduct of such a prospective trial would, of course, take several years. Based on the evidence much of which is discussed above, it is my judgment, given the clinical benefits to patients and the need to reduce costs, viewed against a background of declining drug development in this field, that that evidence is sufficient to support proceeding, if on an experimental basis, with the "shortened trial," as soon as possible.

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July 6, 2017

Comment on Barry Blackwell's Lithium Controversy A Historical Autopsy

I am not an expert on the literature relevant to the discovery and establishment of lithium as a specific treatment for manic-depressive psychosis. I have been asked to comment on the distinct complications that this treatment has posed methodologically for investigators in the field. If one goes no further than the dialogue between experienced clinicians like the late Mogen Schou and JF Cade and clinical scientists, like Barry Blackwell and Sam Gershon, you are easily made aware of the complicated issues they confronted in determining the validity or non-validity of lithium as a prophylactic treatment for any of the affective disorders.

It reminds us that there has been no single way in clinical science to achieve discovery of a new or novel treatment or specifically, a drug. The newly found drugs in the 1950's that revolutionized psychiatry were uncovered by working clinicians in non-controlled clinical settings. These clinicians were, in treating their patients, having little success and very open to testing new agents. The clinicians were, based on their extensive experience with intractable disorders and the response to inadequate treatments, alert to detecting positive effects of a new drug, not immediately visible to less trained eyes. Certain astute clinicians because of this experience were prepared and able to identify promising new treatments when they appeared, for disorders as varied as schizophrenia, depression and anxiety disorders, and also strong enough to then overcome the barriers imposed by establishment psychiatry.

One of those treatments was lithium and its apparent specificity for M-D states. Although no one formula for discovering new drugs exists, we fortunately, have a model for validating in a scientifically controlled short term study or trial, the changes induced by a novel treatment in an acutely, disturbed mental disorder. Although we also have a model for evaluating a long-term treatment, the complications of the long-term course of the illness itself and the lengthy treatment period, in contrast, creates difficult to solve problems for a controlled treatment evaluation.

More concretely, on the critical issue for a controlled evaluation treatment trial of how seriously ill patients in a placebo control group are maintained over an extended clinical trial period, there is as yet no satisfying solution.

These methodological problems have been analyzed in the chapter on Maintenance treatment trials for bipolar disorders" in the volume: Prien & Robinson (eds) "Clinical Evaluation of Psychotropic Drugs" (Raven Press: NY, 1994, pgs. 331-336). The articles in Prien et al. "Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders" (Arch gen Psychiatry 1984, 41:1096-1011), Burgess et al. "Lithium for maintenance treatment of mood disorders", based on the Cochrane Database System Review [(3):CD003013, 2001], and Berghofer et al "Stability of lithium treatment in bipolar disorder long term follow up of 346 patients" (Int J Bipolar Dis, 2013, 1:11),summarize the results of controlled studies up to that time, establishing lithium and the combination with imipramine as efficacious and stable for preventing recurrences of manic episodes and equal to imipramine alone in preventing depressive episodes. And from the Cochrane data analysis, based on nine studies, as efficacious as a maintenance treatment for bipolar disorder, if not for the unipolar form.

These studies follow earlier confirmation that although not universally effective (some 30% of patients do not respond), lithium is efficacious in resolving acute manic episodes.

More recent studies compare newer therapies, such as valproate, which although effective are not found to be superior to lithium and may involve a wider range of side effects.

These studies are by definition difficult to carry off, in view of the time demands and patient selection issues that see too many placebo-treated patients drop out early in the treatment trial. Nevertheless, the findings reassure experts like Fawcett and Goodwin that lithium is probably the most effective treatment maintenance treatment for manic-depressive patients. I see the wide range of studies now available in this area, as providing a network of results and research strategies that can serve as guide and foundation for evaluating new treatments for this chronic disorder.

It appears that the clinicians who uncovered the role of lithium and the clinical investigators who were successful in developing controlled trials for its assessment, should now be more in accord about the strengths and weaknesses of this treatment going into the future.

BOOKS

Comments on Per Bechs's Clinical Psychometrics

There are several somewhat unusual aspects to Per Bech's book on Clinical Psychometrics. First, despite the great need for a historical treatment of how the relatively new science, neuropsychopharmacology, developed quantified methods for psychopathology and the capacity to measure treatment-induced change, no one has come forth to do this important job. Bech not only provides the historical perspective but he manages by surveying recent research to sort out the various rating and other psychological methods that have been developed over several decades, highlighting the continuing controversies that exist in regard to measurement strategy and technical details that underlie method development. We expect a psychologist to write this type of book. It is unusual of course that Bech as a psychiatrist, has fortunately, most of the skills to carry off this very complicated task.

This is not a book, however, that psychiatrists will rush to buy. They are not generally comfortable with quantifying their clinical judgments and have rather little exposure to any training in this area. Contrary to the general belief that psychologists have paved the way for the construction and acceptance of rating methods in clinical research, Bech presents another view. He identifies Kraepelin and Hamilton, two of the most prominent psychiatrists on the world scene as the leaders here. By making a case for that conclusion, he might inadvertently enlist a great many psychiatrists in the further development of this field. Bech actually balanced this view in the text, by also describing the prominence of Galton, Spearman, Eysenck, the contributions of Maurice Lorr and John Overall, and several other psychologists. To fully appreciate what is covered, e.g., which scales are currently available and what they are capable of measuring, we note the clarity with which he presents this information and his particular perspective on the right kind of strategy and associated technologies for constructing these instruments.

Bech classifies test development into two periods, the "classical" and "modern." In describing factor analysis, he contrasts supporters of the two factors versus those who rely on rotations and thereby, uncover a multi-factorial structure of psychopathology. Beyond that he cites limitations of factor analysis, generally, pointing out that it cannot be used to validate phenomena, but more

importantly, is not designed to develop methods, but only to provide classification of variables. He appears to be convinced that the age of factor analysis is over, and that the field should move on the use of the "item response" model. He sees the latter method as better suited to solving the problems in this field. I am not sure here, however, that his glossary definitions of "validity" which stress clinical significance and unidimensionality, correspond to the commonly accepted psychometric definition; i.e., the simpler notion that validity is the extent to which a method measures what it purports to measure, I, therefore, think I understand his stance on the number of factors, but take issue with his conclusion. He like Max Hamilton and Pierre Pichot appear committed to brief scales and the two-factor approach. Those on the other side of the issue conceive of each of the disorders as multifaceted and utilize factor analysis to uncover their dimensional structures.

Thus, the factor analysts view it as a data reduction method aimed at uncovering the two or more components that can most parsimoniously explain what the method is actually measuring. Further, when the disorder is conceived to be multidimensional it is then necessary to identify each of the components, and from the factor analysis results, create ways of quantifying them. Currently that is done through principle components analysis and rotation. Bech presents thoughtful views on these matters but does not do justice to the multifactor approach. A historical example of the contrasting lines of thinking here are where he focuses on the Hamilton Depression Scale (Ham-D) and the Brief Psychiatric Rating Scale (BPRS), brief scales, but provides limited information on their predecessors, the Wittenborn Psychiatric Scales and Lorr's Inpatient Multidimensional Psychiatric Scales, both multifactorial scales. In these two cases, the authors' targets were the facets of psychopathology and the importance of developing a set of items for each of these facets. The basic psychometric principle followed was that more reliable and valid measures of the components, e.g., "anxiety", can be achieved by having the judges rate a set of observed behaviors that reflect that component, than by having an observer rate a more complex, global concept such as "anxiety". It was Lorr, as Bech points out, who wrote and compiled the 63 items and determined the factor structure of psychopathology. Overall and Gorham used Lorr's factors to craft global definitions based on interpretation of his factor items, in order to create their 16 "global" items for the original BPRS. We are aware of how well the BPRS used in hundreds of studies, worked these many years, particularly in the evaluation of change in overall severity of the disorder in drug trials. But when it comes to reliably and validly measuring the dimensions of psychopathology, equally important in the science, the IMPS is a more effective instrument and applicable to a wider

range of problems in clinical research.

This was perhaps the only shortcoming I could find in this otherwise balanced and clear-headed judgment of the major issues in our field. For psychiatry, Bech highlights in reviewing the history of the rating scales, that Kraepelin constructed his own rating method, to be followed by scales developed and modified by Max Hamilton and Pierre Pichot, all three attempting to create a functioning science for psychiatry. Their focus on the importance of scales will no doubt surprise psychiatrists and may prove a positive influence on their approach to them in clinical practice. The history Bech presents is inspiring. Not only does he elevate rating scales in the minds of researchers and clinicians but he also, following philosophers Jaspers and Wittgenstein, in restoring respect for the phenomenologic approach to characterizing the nature of psychopathology.

I heartily recommend this book as a text for Clinical Methods courses for psychologists and psychiatrists. I view Per Bech's effort as filling a significant gap in the practice of current clinical research and an important contribution to the science of psychopathology.

August 1, 2013

Response to Donald Klein's Answers to Martin Katz's Questions Related to Klein's Response to Katz's and Bech's Reply to his Comments on Bech's Clinical Psychometrics

Don Klein cites a valid concern about "semantic slippage" when moving from one context to another with various statistical approaches. So, he believes that despite the selection of the most mathematically based factor analysis technique, principal components, there is "ample grounds for disagreement" about the extent of interpretation involved. Although it can be true that "each loaded variable is a composite of correlated variables, each with… an ambiguous label," it is also true that with certain techniques, the labels or items involved can be unambiguous and straightforward in content.

In support of my earlier statement that interpretation was minimal with the principal components procedure, I was referring to such examples generated from observational and self-

reported mood inventories as “depressed mood-motor retardation.” That title was for a component from our own work, that had in its high loading clusters such items as “looks sad,” “reports feeling down,” “blue,” “motor movements slowed down,” etc., where the additional variables in the component add reliability but no further conceptual complexity to the component. Nevertheless, the dimensions derived with principal components can get somewhat more complicated in concept so he has a basis for requiring more attention to the degree of interpretation involved in any example, even of this type.

He then questions in regard to the mixture issue, “Can dimensions be independent but nevertheless have interactions?” To answer this query, one has to step back and examine how the “dimension” is derived. It is originally composed of parts that are shown to be highly linked, with each part having a similar pattern of relationships with other variables that may be part of other dimensions. For example, despite forming the parts of the” anxiety-agitation-somatization” dimension in our work, we note that each part has its own pattern of relationships with variables that make up the composition of other independent dimensions, e.g., anxiety, in itself, a component of psychopathology across most all mental disorders, is known from many studies to correlate significantly (>0.50) with “depressed mood “and with “hostility” (>0.40), items representative of other dimensions. The opportunities for interaction of key parts of different independent dimensions are, therefore, multiple. That is what we found in our studies and was elaborated on in the “Depression and Drugs” book.

The interactions in those studies were clear and led to the “opposed emotional states” hypothesis. We believe that the interactions of these states helped to explain, in great part, the psychological turmoil and general stress undergone by the patient. Note that there was no attempt with the principal components analysis to “produce results equivalent to a model of latent categories.” The aim in that study was not to uncover new “diagnoses,” new subcategories of illness, but to identify and describe the dimensions of psychopathology that structure the “major depressive disorder.”

Klein provides an interesting discussion of Chassen’s intensive research design. It reminds us that earlier, there were alternative approaches to the currently established model for clinical trials. It is a much more satisfying approach to drug evaluation for the experienced investigator than the mechanical quality associated with the current established model, which relies less on the expert, more on the trained rater. This alternative approach was not taken up by many and is now

rarely used because of the intense monitoring and the expertise required of the clinical investigators in the conduct of such studies. He also notes that we were still unable to predict response to any of the drug classes, i.e., which patients respond to which drugs. Despite its scientific advantages, the expense to conduct the intensive trial makes the current established model look more feasible and more modest in its overall costs. Others have advanced ideas to improve the current model.

The Depression book provides another alternative, also, applied in earlier trials. The "componential" model of antidepressant clinical trials includes the use of the established trial's Hamilton Depression Rating method for evaluating overall "efficacy," but goes further to profile the specific clinical and psychological actions of the experimental drug. The latter step which requires little additional expense greatly expands the amount of information that can be retrieved from the study of a new treatment, and makes possible the uncovering of actions that although not applicable to the target disorder, may uncover drug actions that are applicable in the treatment of mental disorders, other than depression, e.g., anxiety or phobic disorders. The "intensive design" has a distinct place in the clinical evaluation of new drugs. It still, however, does not achieve what is even more essential when carrying out a major drug trial, that is, the uncovering and quantifying of the specific clinical and psychological actions of the new drug, something that none of the current approaches, including the established model endorsed by the FDA, make a serious attempt to accomplish.

June 5, 2014

Comments on Martin Keller's Clinical Guide to Depression and Bipolar Disorder: Findings from the Collaborative Depression Study

The authors' description of the inception, results and impact on psychiatry and psychopharmacology of the NIMH Collaborative Depression Study, as presented in this recent book, is sharp and greatly informative. The study was started by the Institute's Clinical Research Branch in 1970 to deal then, with essential unresolved problems in nosology, genetics and pathophysiology. It was to expand greatly over the years, resulting in major contributions to the understanding of long term course in depression and to the development of the Research

Diagnostic Criteria (RDC). The RDC was to serve later as the basis for the radical revision of the diagnostic system, the creation of the operationally defined DSMIII. The Study's successes resulted in receiving grant support for several decades so that by 2010 it was still in operation recruiting new investigators and producing important findings on the longitudinal course of the disorder, leading to several scientific awards. Notably, it was conducted alongside an equally ambitious Biological Collaborative component, initiated at the same time, to test the then new hypotheses concerning the nature of the disorder, e.g., the "catecholamine hypothesis," and to uncover the specific relationships of neurochemistry and behavior that are presumed to represent underlying mechanisms of the disorders.

Between them the two Collaborative efforts have resulted in several hundred publications produced by a range of authors representing several disciplines in neuropsychopharmacology. Keller in his emphasis on description of the book's content, omits discussion of the contributors who participated over the decades in the conduct of the study. Regarding its initiation as, he states, an outgrowth of the NIMH 1969 Williamsburg Conference (Williams, Katz, Shield (eds), Recent Advances in the Psychobiology of the Depressive Disorders. GPO, Washington DC, 1972) the planning group for the Study included such historical figures as Eli Robins, and George Winokur and was chaired by James W. Maas. Bob Hirschfeld, who was later to become coordinator of the Clinical Study, describes well this history in the Introductory Chapter. Of critical importance to its beginning were the roles of Gerald Klerman, Bob Spitzer, and Jean Endicott. Gerry and I, as Chief of the Clinical Research Branch, co-chaired the Clinical Committee, but it was Klerman who sparked the effort and with his unequalled administrative skill managed to keep it on track for many years. Alongside him, monitoring every element was Jean Endicott, a co-editor of the volume. The early "young" co-investigators included such notable figures in our fields as Jan Fawcett, John Davis, Nancy Andreason, Bill Coryell (a co-editor}, Tom Williams, Joe Mendels, Robert Shapiro, Jack Croughan, Paula Clayton, Regina Casper, John Rice, Ted Reich.

In addition to its contributions to the research literature and to clinical practice generally, the Collaborative studies made a major contribution to the training of young, primarily, psychiatric investigators in the methodology of clinical research and helped to prepare them for careers in research. Little is more important for advancing the field and elaborating on its history than these kinds of accomplishments.

A word should be said for the contribution of the NIMH to this long term, complex program of research. The Institute is looked to primarily, almost solely, for its financial support of independent research. In the case of the Collaborative Studies, it deserved credit for recognizing that clinical, unlike basic research, requires a more active role, that is, mechanisms to identify critical unresolved obstacles in order to move forward in this important area of research. In that case, having a national conference to identify the problems, it was then able to move ahead and actively organize strategic studies to solve the focal problems. Fortunately, today, the current Director has a comparable vision and has shown his respect for the role of history in their current efforts to resolve similar problems in clinical research.

July 3, 2014

PERSPECTIVE

Comment on Thomas A. Ban's RDoC in Historical Perspective

Samuel Gershon's question

The Research Domain Criteria (RDoC) program recalls an earlier time, the early 1970's, when the NIMH sought to launch an ambitious collaborative program on the psychobiology of depression, designed primarily to test the then new hypotheses identifying the role of dysfunction in central neurotransmitter systems. In view of the variations in the diagnostic systems applied at that time, and the resultant ambiguities in language, a diagnostic system applicable for research was required that would be more reliable and generalizable across studies. To render the then controversial and unreliable diagnostic system suitable for research, a group led by Eli Robins, Robert Spitzer and Jean Endicott, was convened by the NIMH's Clinical Research Branch to refine

the definitions so that reliable operational criteria could be articulated for each of the categorical diagnostic types. This contracted effort resulted in the "research diagnostic criteria," the RDC, published by Spitzer et al. (1979). In addition, a data collection instrument was constructed that would ensure that all domains and criteria of psychopathology would be covered in the diagnostic interview, the "schedule for affective disorders and schizophrenia," the SADS (Endicott and Spitzer, 1989).

The RDC provided the structure for the then developed DSM III, an empirically derived, presumably, a theoretical system, designed to be more reliable than previous systems applied in psychiatry. Spitzer, a developer of the RDC was selected to serve as Chairman of the Classification Committee that then created the DSM III. In today's view, the RDC could be construed as a more elementary version of the currently proposed RDoC, and thus, a precursor of the RDoC. It relied on traditionally accepted symptoms, then articulated them more explicitly, thus, increasing their reliability as elements to be utilized in the structure of the system.

The field was not yet ready to define the underlying mechanisms of the disorder or drug actions in terms of dysfunction in neurochemistry or associated neural circuits or genetic bases. Applying the RDC to research on the psychobiology of depression as conducted in the collaborative (Maas et al., 1980) and other programs during this period, permitted significant advances in the science and in psychopharmacology, assisting in identifying relationships between the neurochemistry underlying the diagnoses and the behavioral elements that contributed to the symptomatology of the categorical disorders.

Nevertheless, as Maas and I pointed out (1994), the diagnostic system fell short of advancing the science beyond a certain point, and could in fact, be an obstacle in attempting to uncover the neurobehavioral mechanisms underlying the disorders and the bases for the efficacy of the established antidepressant agents. We contended then, that the components or dimensions that structured the disorder, along with the effects on central neurotransmitter systems, should be the starting points for these types of investigation and not the more complex, still partially understood diagnostic types. We demonstrated how that substitution worked in Katz et al 1994, a study that linked drug-induced changes in metabolites of serotonin and norepinephrine with different changes in components of behavior and mood, e.g., 5-HIAA with changes in anxiety, MHPG with motor activity. Again, I see these earlier findings now as further evidence that relying on diagnosis as we knew it then, as central to uncovering basic information about the disorders or

their reactivity to chemical agents that impact central neurotransmitter systems, was the "wrong" path, incapable of resolving problems in this realm of research. We proposed at the time to set diagnosis aside, to adopt in its place a componential or dimensional approach to defining psychopathology, in order to advance science in this area. In that case, based on an intensive analysis of a large multisite patient sample, we identified as major dimensions for depression, depressed mood-retardation, anxiety-agitation-somatization, and hostility, with additional components from disturbances in motor activity and cognitive impairment. Today the Insel-Cuthbert RDoC approach leads to a somewhat similar structure on the behavioral side, but looks much beyond the neurochemical framework we applied in the 1970s and '80s. They have included more recent work on neural circuitry and genetics and provided space for expected further advances in these areas.

Their proposal and the target they are working towards in the matrix is a bold attempt to provide a set of long term goals, a structure to guide future research, while releasing the field from its decades-long reliance on an inapplicable diagnostic network. I admire the effort and with them, believe that it is the proper direction and further, that theirs is a well thought out plan to achieve its aims.

Achieving their goal of completing the matrix is, however, a work in progress and the long-term goals still well beyond their grasp. The pressing question we face today relates to investigations in the here and now. How do investigators deal with the traditional centrality of diagnosis in clinical research, generally, and in clinical trials, specifically, in the interim, i.e., in the meantime, while we await the long-term goals of the RDoC to be achieved?

My recommendation is straightforward. It is that the RDoC program continue as it has, to integrate current advances in neurochemistry, molecular biology, neural circuitry, genetics into the matrix columns. To effect associations with clinical phenomena, with psychopathology the program needs, however, to take another path. Why not adopt the dimensions, the componential approach that have already been developed as the central clinical phenomena, those facets that are currently capable, as evidenced in psychometric research, of being measured validly? As one example, I refer to the system that my colleagues and I developed and is now well represented in several publications (Katz et al., 1984, 1994, 2004; Katz, 2013). These studies identifying well-established reliable, quantitative dimensions, have already been applied in several areas of clinical research, specifically, in the creation of a new, componential model for the clinical trial of putative

antidepressants. This system based on these earlier studies can be productively applied to a range of new work in these areas and serve well in this field while we await further progress of the RDoC program.

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Comment on Jose de Leon's article "Focusing on drug versus disease mechanisms and on clinical subtyping to advance personalized medicine"

Jose de Leon's editorial on "Focusing on drug versus disease mechanisms and on clinical subtyping to advance personalized medicine," published in *Acta Neuropsychopharmacologica*, in 2014, is a very thoughtful piece and an eloquent case for the importance of sophisticated clinical experience and judgment in advancing the science of psychopathology. The author wishes to rescue psychiatry from its need to emulate other specialized areas in medicine and its conception of its disorders as "diseases." Schizophrenia and the affective disorders are not as far as we now know, based on established brain neuropathology and thus, do not qualify as diseases. If we adhere to the tenets of descriptive psychopathology, they are syndromes. Reliance on the DSM undermines that approach, and consequently, is viewed as an obstacle to progress in advancing the science. He would, in his long-term goal for "personalized medicine," propose the syndrome approach in place of the conventional diagnostic system. In advocating this approach, he points to the neglected early work of Leonhard in characterizing the syndromes and the efforts of others to apply a more empirical analysis to the issues of classification.

I believe with De Leon that psychiatry should cease trying to emulate other medical specialties. It does not have diseases, based on defined neuropathological processes, to target. It has, at best, syndromes with continuing disagreement about their borders and somewhat resistant to quantification that makes progressing in the science difficult. Even where we have "disease", such as with Alzheimer's, the disease approach, as the author notes, has not been very successful in uncovering new treatments.

The author would have us step back, rely more on "descriptive psychopathology," the basic science for psychiatry as Ban (2007) and others have proposed. It will permit taking advantage of sophisticated clinical judgment as against the present obsession with controlled trials and the DSM. It is clinical judgment that led to the discovery of the new drugs. It should be made easier for "clinical experts" to continue to make their mark in this field.

Regarding goals and personalized medicine, I would, however, propose taking an even further step back from the syndrome approach. The prime goal should be to further advance the science of psychopathology. To do that one has to adopt an even more elemental approach to the

more complex syndromal, which in itself can be difficult to quantify. It is necessary to start with identifying and validating the emotional, cognitive and behavioral components and the dimensional constructs, already demonstrated quantifiable entities, upon which the science can be built. There is already much evidence that this approach is capable of opening new pathways in the science, resulting in uncovering the structural nature of the depressive disorders and in elaborating the nature, timing and mechanisms of actions of established drug treatments. My own effort in advancing this approach is one example (Katz, 2013). The componential system needs to be more widely applied and the atmosphere for the kind of thinking De Leon is encouraging more quickly developed.

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August 25, 2016

E-BOOKS

Introduction to An Overview of the First 50 Years Oral History of Neuropsychopharmacology Synopses of the 10 Volumes,

edited by Martin M. Katz

Following the publication of the landmark 10-volume series on the Oral History of Neuropsychopharmacology, Sam Gershon and I proposed to introduce the series to the membership of the American College of Neuropsychopharmacology (ACNP) via a Panel at their

2011 annual meeting. The idea for the 50-year History, recorded on videotape by the founders of the ACNP and by 213 participating members, was first proposed by our esteemed late Executive Director, Oakley Ray. He then left to Tom Ban, the task, who by a Herculean effort brought it to fruition. Tom monitored the collections, selected the interviewers and recruited the interviewees who responded with lively, engaging tales reflecting the origins and high points of a fascinating history in the development of a new science. To consolidate the effort Tom Ban divided the History into sectors covering the various participating sciences and periods of time and then, invited representative figures from those eras to edit each of the volumes.

There is no way to briefly summarize the some 213 interviews, but we thought it highly useful to call to the attention of our membership the availability of this remarkable tour through the History of an exciting field. The members have been part of a revolution in the treatment and reconceptualization of mental disorders and have helped to open new vistas in the brain sciences.

In introducing the volumes, we asked for the purposes of the 2011 Panel, six of the Editors or a Representative of that era, to describe briefly the contents of their volumes. Later, in preparing this overview we decided it more appropriate to include brief descriptions of all of the volumes, so that the reader can not only receive the full picture, but also have a ready reference source from which to locate each and every one of the 213 interviews. Following each volume description, the chapter, includes a Table of Contents for that volume, identifying each of the interviewees and the interviewers

As always with such overviews, we seek to make ACNP members aware of this unique, valuable source for future research in our field and trust that they will find great satisfaction in reviewing their own, and their esteemed colleague's views and visions; perhaps, to ponder on how fortunate they were to have participated in this great adventure in science.

December 5, 2013

APPENDIX

Biographic Sketch

Martin M. Katz received his A.B. degree in Chemistry at Brooklyn College and his Ph.D. from the University of Texas in Psychology and Physiology. From 1958 to 1968, he served in the National Institute of Mental Health (NIMH) as Executive Secretary of the first Psychopharmacology Advisory Committee, then, in 1965, as Head of the Special Studies section in Psychopharmacology. In 1968, he was appointed Chief, of the NIMH Clinical Research Branch, a new program charged with expanding research on the causes and treatment of schizophrenia and the affective disorders. It initiated national conferences and developed Collaborative Programs on the Psychobiology of Depression, laying the groundwork for the new Diagnostic and Statistical Manual (DSM) and large-scale testing of the new biochemical theories of the genesis of the disorders. The Biology and Clinical Collaborative Programs, created by Dr. Katz and Branch Staff (1970-1978), were responsible for the training of many young investigators, and provided needed methodology for expanding research in these fields. The Clinical Aspect of the Program was still, thirty years later, in operation under an NIMH grant. In 1984, he joined the Psychiatry faculty at Albert Einstein College of Medicine as Professor, establishing the first Division of Psychology and Laboratory of Psychopathology at the College. Since 1996, he has been Adjunct Research Professor in the Department of Psychiatry, University of Texas Health Science Center at San Antonio, where he has conducted grant-supported research on the “Biological Aspects of Depression” and the neurobehavioral mechanisms of action of antidepressant drugs.

March 3, 2016

Curriculum Vitae

PERSONAL

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EDUCATION;

Brooklyn College: Chemistry/Psychology, A.B., 1949

University of Texas, Psychology, Ph.D., 1955

MAJOR PROFESSIONAL POSITIONS

Currently:

Adjunct Professor, Department of Psychiatry, University of Texas Health Sciences Center at San Antonio

Formerly:

Professor and Chief, Division of Psychology, Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, 1984-1994

Clinical Professor, Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, New York, 1994-2004.

Adjunct Professor, Department of Psychiatry and Behavioral Sciences, George Washington University Medical Center, Washington, DC, 1982-1990

Chief, Clinical Research Branch, National Institute of Mental Health (NIMH), Bethesda, MD. 1968-1978

Chief, Special Studies Section, Psychopharmacology Research Branch, National Institute of Mental Health, Bethesda, MD, 1965-1968.

Research Psychologist, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, MD, 1960-1964

Executive Secretary, Psychopharmacology Advisory Committee, National Institute of Mental Health, Bethesda, MD. 1957-1959

PROFESSIONAL SOCIETY MEMBERSHIPS

American College of Neuropsychopharmacology (Life Fellow, Emeritus Vice President)

Collegium Internationale Neuropsychopharmacologicum (Fellow, Emeritus)

Association for Psychological Science (APS)

AWARDS and HONORS

Citation Classics, Social Science Citation Index, *Current Contents,* 1981 (Methods for Measuring adjustment and social behavior in the community, *Psychological Reports Monograph*, 1963)

Administrator's Award for Meritorious Achievement, Alcohol, Drug Abuse and Mental Health and Human Services, US Government, 1979

Vice-President, American College of Neuropsychopharmacology, 1978

Nominee, Stanley Dean Award for Research on Schizophrenia, 1977, 1978

Member, Council, American College of Neuropsychopharmacology, 1972-1974

Research Fellow, Culture and Mental Health in Asia and the Pacific Program, East-West Center and University of Hawaii, 1967-1968

Panel honoring Pioneering MMK's Research in Depression, American Psychological Association Annual Meeting, 2011

EDITORIAL BOARDS

Formerly:

Associate editor: Journal of *Integrative Psychiatry*

Member Editorial Board*, Neuropsychopharmacology*, Journal of the American College of Neuropsychopharmacology.

Member, Editorial Board, *Psychopharmacologia.*

Member, Advisory Editorial Board*, Contemporary Psychology.*

Member, Editorial Advisory Board, *Schizophrenia Bulletin.*

Member, Editorial Review Board, Journal of *Psychedelic Drugs*.

OTHER PROFESSIONAL ACTIVITIES

Co-Director, World Health Organization (WHO) Field Research Center, Queens Medical Center, Honolulu, Hawaii-1980-1990

Consultant, Division of Mental Health (WHO) -1978-1992

Chairman, Subcommittee on Methodology, WHO Advisory Committee On Alzheimers Disorder, 1997-1998.

Representative Committee Activities

Member, Advisory Committee, NIMH Collaborative Research Program on the Psychotherapy of Depression, 1982-1990

Advisory Committee, WHO International Pilot Project on Schizophrenia (Nine Country Study), 1975-1984

Planning Committee, The National Neuropsychiatric Institute, WHO Collaborative Center for Research and Training in Mental Health, Aro, Nigeria, 1980a: Convened to develop first training institute for neuropsychiatry in Africa

Research Advisory Committee, NIMH, 1976-1978

Advisory Committee on Research, New York State Department of Mental Hygiene, 1972

Co-Chairman, NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression, 1972-1986

Chairman, NIMH Research Task Force Committee on Mental and Behavioral Disorders, 1973-1975

RESEARCH GRANTS

Co-Principal Investigator, Biological Aspects of Depression and Antidepressants. Department of Veteran Affairs, University of Texas HSC at San Antonio, 1996-2003

Principal Investigator, Video Methodology for Estimating Onset of Antidepressant Actions, Pfizer, Inc., 1998-1999

Principal Investigator, NIMH-Clinical Research Branch Collaborative Program of Psychobiology of Depression, Biological Studies Program, Albert Einstein College of Medicine/Montefiore Medical Center, 1984-1993

Co-Principal Investigator, NIMH-World Health Organization Determinants of Outcome of Severe Mental Disorder. Queens Medical Center, Hawaii, 1980-1986

FIELDS OF PRESENT MAJOR SCIENTIFIC INTEREST

Psychopathology (Depressive Disorders), Psychopharmacology (The Mechanisms of

Antidepressant action and the Methodology of Clinical Trials of New Agents),

Cross-Cultural Studies

June 18, 2015

Representative Publications

BOOKS

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