

## **In Memory of Hagop Souren Akiskal (1944 – 2021)**

**By**

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On January 20, 2021 Hagop Souren Akiskal, a member of our International Network for the History of Neuropsychopharmacology (INHN), passed away. Born on January 16, 1944 in Beirut to American parents, at the time of his death he was 77-years-old.

Hagop Akiskal grew up and was educated in city of his birth. After graduation from the Medical School of the American University of Beirut in 1969, just about the end of the Lebanese Civil War, he moved to the United States and completed residency training in psychiatry in Madison at the University of Wisconsin. His rotations in substance abuse and student health stimulated his career-long interest in mood disorders (Blackwell 2011a,b).

After completing residency Dr. Akiskal started his professional career in Memphis, in the Department of Psychiatry, University of Tennessee. He moved up rapidly on the academic ladder to become Professor of Psychiatry and Pharmacology within eight years, at the age of 33. His research focused on the nosology and treatment of patients in the Mood Disorders Clinic where thousands of patients were seen without a single suicide, perhaps because of the close attention to family and social issues. He also worked in the sleep laboratory studying the neurophysiology of dysthymia and its response to antidepressants (Blackwell 2011a,b).

Following several years at NIMH (1990-1994) he became Director of the International Mood Center at the University of California at San Diego. The title reflects a career-long involvement in international research and education. Fluent in five languages he has held consultant or editorial posts and distinguished lectureships in Switzerland, Canada, Greece, Hungary, Russia, Germany, South America, Italy, Spain, Sweden, Lebanon and England (Blackwell 2011a,b).

Searching for a unifying hypothesis of affective disorders (Akiskal and McKinney 1978) *Hagop Akiskal*, in his life-time research, studied sub-affective disorders, such as dysthymia, cyclothymia and bipolar II disorder in the “borderline realm” (Akiskal 1981) In 1983, he critically reviewed the relationship between personality and affective disorder (Akiskal, Hirschfeld and Yerevanian 1983) and presented his findings on the psychopathology of chronic depressive subtypes (Akiskal 1983). In the 1990s, pursuing the same line of research further, he introduced the concept of “bipolar spectrum disorders” (Akiskal, Maser, Zeller et al. 1995), provided evidence for switching from unipolar to bipolar II disorder (Akiskal and Pinto 1999) and described prototypes of bipolar I, II, III and IV disorders (Ban 2011a,b).

As Editor of the *Journal of Affective Disorders* Hagop took particular pride in helping young investigators achieve publication and in sustaining a broad perspective that includes biology, genetics, neurophysiology and long-term outcome studies. But what Hagop Akiskal considered his greatest achievement was “to bring smiles to the faces of people... I never saw a smiling face when I was growing up. People were all talking about genocide, how much pain they had that they could never give up” (Blackwell 2011a,b).

As both educator and researcher Dr. Akiskal attributed his influence to the close attention he paid to family and patient concerns reflected both in an interest in public education (initially at NIMH) and numerous awards including several as “teacher of the year” and the Gold medal from the Society of Biological Psychiatry for pioneer work with affective disorders (Blackwell 2011 a,b).

For the Oral History series of the American College of Neuropsychopharmacology, Akiskal was interviewed by Paula J. Clayto, in Scottsdale, Arizona, on December 9, 2008. The full text of this interview is presented below (Ban 2011a,b).

PC: My name is Dr. Paula Clayton and I will be interviewing Dr. Hagop Akiskal who is a distinguished member of the ACNP. The date is December 9, 2008 and we’re at the ACNP meeting in Arizona. So, Hagop, tell us about your background, your family and how you got to where you are today.

HA: As far as background, I am of Armenian origin, born in Beirut, Lebanon, just when the French mandate was ending and Lebanon had become an independent country. I grew up in a

multicultural, multi-religious atmosphere. My father and his family were all in engineering fields, and my mother's side in journalism, literature, teaching, and medicine.

PC: How did that influence you?

HA: I have been asked this question before, I therefore have had the opportunity to think about it at some length. I believe I "inherited" literary talent and a penchant for medicine from my mother's side and the precision that characterizes physics and math from my father's lineage. This dual heritage may explain the clarity of thinking and persuasive prose that made me a highly cited clinical scientist and eventually a good editor.

PC: How about schooling?

HA: In those days Beirut was considered "the Paris of the Middle East," a comparison that meant to capture the sophisticated culture that characterized that vibrant city. I attended a private Armenian school whose principal, educated at the Sorbonne and Oxford, was renowned for his "tough-minded" approach, combining a liberal humanistic education, including four languages, with a rigorous exposure to the sciences. I then did a year of mathematics - my father had been killed in a car accident and some in my family wanted me to consider electrical engineering - all of this preceding my enrollment at the American University of Beirut; if it weren't for that I wouldn't be in the United States.

PC: Why do you say that?

HA: Because if you go to a university and medical school of the high ranking of the American University of Beirut, it's natural to come to the United States.

PC: From your history it followed without interruption. You graduated with honors didn't you?

HA: I did, Alpha Omega Alpha.

PC: Then you came to Memphis?

HA: That's correct.

PC: Tell me how you made that decision, because there were many others from that university who went to other places?

HA: I applied to the University of Washington in Seattle, Tulane and to New York Medical College. On paper, however, the University of Tennessee, Memphis seemed the most solid for a clinical residency, which was flexible for research experience.

PC: Did you interview with others, or just do this all by paper?

HA: I didn't interview with anybody, I was accepted, via correspondence, almost as soon as I applied for residency positions at Memphis and at Tulane; Seattle, too, was very much interested in having me; New York had invited me for an Interview. After wavering between Seattle and Memphis for a week - I had had professors in Beirut who had trained or had spent sabbaticals in these two medical centers - I made up my mind for Memphis, and after the ECFMG exam, and the requisite visa formalities for foreign medical graduates, when the time came, I boarded the plane and started the long journey to Memphis. I had never lived - or traveled away - from my family before.

PC: Oh, my goodness! And, you spoke English when you came?

HA: Of course.

PC: You speak many languages?

HA: Five.

PC: So, you came to Memphis and started your residency.

HA: That's correct.

PC: Did you finish it there?

HA: No, I went to Wisconsin for my third year.

PC: Tell us about that transition.

HA: I had the good fortune of being tutored by Rafic Waziri in Memphis, who was originally from Afghanistan. He was in the first class that was exposed to a neuroscience course in Boston under Eric Kandell and the private weekly seminar with him was a very important introduction to the brain. In 1970 not too many places were teaching neuroscience. Dr. Waziri, a perfect gentleman, was a tough-minded psychiatrist, vintage George Winokur.

PC: At Washington University?

HA: No. He took a faculty position in George Winokur's department at the University of Iowa. When we met he was in Memphis for two years in transit to Iowa.

PC: Is he the one who first got you interested in mood disorders?

HA: Not entirely. He largely exposed me to the elegance of scientific methodology in psychiatry along biological lines. Parenthetically, the monograph on manic depressive illness by Winokur, you and Reich, which I read in 1969, was a major source of inspiration for me.

PC: But then you declared an interest in mood disorders very early.

HA: Actually, it's much more complicated than that.

PC: Okay, tell us.

HA: At the American University of Beirut, I had the good fortune of being exposed to Dr. Vahe Puzantian, a superb clinician, an Edinburgh-trained Lebanese-Armenian psychiatrist, who had been a disciple of Frank Fish: Fish had published great monographs on phenomenology and schizophrenia, which I read as an intern, underlining in red every other line! Thus, I did arrive at the United States with an interest in Kurt Schneider, Karl Jaspers and their approach to schizophrenia. Emil Kraepelin had been another major influence. While in Lebanon, as a fourth year medical student, my first psychiatric patient presented with catatonia and he made a miraculous recovery with perphenazine. That was a remarkable situation for a fourth-year medical student to observe first-hand, a patient, in a state of stupor, with all the dramatic signs of catatonia, recover on a high potency neuroleptic within few days.

PC: So that stirred your interest?

HA: It reinforced my interest in psychopharmacology, which was a subspecialty I was considering concurrent with training in psychiatry. However, my interest in schizophrenia was soon to erode. When I came to the States in 1969, most patients with psychotic disorders were diagnosed “schizophrenic,” which was at odds with what I had been exposed to in Lebanon, where psychiatric thinking, along the then British model, was oriented towards manic-depression. So, for a while I shifted to psychedelic substance abuse, there was an epidemic of it in those days, and from there to student mental health. I went to Madison, Wisconsin to have exposure to that.

PC: To student mental health?

HA: Yes, but I was interested in many other things Madison offered, such as social psychiatry, Seymour Halleck, consultation-liaison, David Graham, as well as primatology and experimental psychopathology, Harry Harlow, William Mckinney, Lorna Benjamin. When I rotated in the student mental health clinic, it appeared to me that a lot of it represented affective disorders. So, when I returned to Memphis, it was natural that I would start a mood clinic.

PC: When was that?

HA: Although there existed, several lithium clinics in the US, the clinic I was interested in was broader than that. It was one of the first mood clinics, if not the first, in 1973. We started where Washington U left off and where, eventually, I had to meet you and your colleagues. Wash U studied the major syndromes, with a few exceptions. You guys had pioneered in the systematic study of the major syndromes that were already reasonably well characterized in your department,

so I decided to study those patients with fewer symptoms, who fell short of either the full syndromal criteria, or the duration criteria, the “undiagnosed” in the St. Louis framework. Very few people were studying these conditions systematically, so I ended up making a whole career of doing so. The outpatient departments in community mental health centers were full of them.

PC: When did you publish the article on depression with McKinney?

HA: That was in *Science*, 1973. I must mention what a great mentor Bill Mckinney was, who had been himself tutored by Morrie Lipton and Art Prange at Chapel Hill.

PC: Were you back at Memphis when you wrote the *Science* paper?

HA: I had done that work in Madison.

PC: So that was your major publication during that period?

HA: Actually, I also wrote a provocative paper entitled “Psychiatry and Pseudo-psychiatry,” which was published in the *Archives of General Psychiatry*. I had seriously considered leaving psychiatry, but these two papers were key in outlining what I would pursue in psychiatry.

PC: When was that critique published?

HA: Six months earlier than the *Science* paper.

PC: Okay.

HA: The *Science* paper was one of the rare publications written by a psychiatric trainee, attempting to bridge the gulf between psychology and biology and documenting the then sparse data on their interaction and made a major impact. It’s highly cited, and was required reading in psychology and psychiatry for many years – it still is in many universities.

PC: Right.

HA: The United States is a remarkable country.

PC: Why do you say that?

HA: Because if you publish in the United States, the whole world knows about it. I remember a week after the *Science* paper appeared, I received a reprint request from then Leningrad, now St. Petersburg, because we had cited several Russian pharmacologists, like Lapin and Oxenkrug, who had written about serotonin. You would recall, the US was catecholamine-focused then.

PC: That reprint request was even before e-mail or the Internet.

HA: Absolutely, 1973. The visibility is much more today, but for a psychiatrist to publish in *Science* was equally unusual.

PC: It was wonderful. I remember that paper. The other thing I remember is the paper from the outpatient clinic on cyclothymia and its outcome. When was that published?

HA: 1977.

PC: Tell us about between 1973 and 1977.

HA: Publishing was slow; we were collecting data in the clinic. These were long-term prospective studies and took a few years to collect all the data. I also did biological work, especially along psychopharmacotherapeutic lines; psychopharmacology was not formally taught in those days.

PC: We were just discussing that at an ACNP seminar.

HA: I learned it by doing it and, even as early as a second year psychiatry resident, I was teaching psychopharmacology to my peers in psychiatry.

PC: I wonder who replaced you when you went to Wisconsin.

HA: Waziri was still in Memphis, but soon he left for Iowa. Eventually, when completing my psychiatric training in Madison and returned back to Memphis, I was given joint faculty appointment in psychiatry and pharmacology. When I taught psychiatry in the clinical years, medical students had already been exposed to my lectures in psychopharmacology during the basic science course of pharmacology, as a result many signed up to do research electives with me in the mood clinic in their senior year.

PC: I didn't realize that.

HA: I eventually taught psychopharmacology to pharmacy and nursing students, as well as neurology and internal medicine residents. This had the net effect of reinforcing the view that psychiatry had come of age and had to be respected as one of the major branches of medicine and basic science, without losing its broad psychosocial, cultural and humanistic roots.

PC: That's a good message to send.

HA: The students heard the same guy who taught pharmacology, later teaching psychiatry. That had a great impact.

PC: You were more credible.

HA: Absolutely. I was the only psychiatrist who was appointed to various medical school committees.

PC: You also had another physician psychiatrist who was a mentor in Tennessee, didn't you?

HA: That was my first Chairman and Professor, the late Garabed Aivazian, who had been trained in Lebanon, Paris and Cornell. His successor, William Webb, was also a great supporter of my endeavors in research and University-wide activities

PC: Right, and who both supported you to start the mood clinic?

HA: Yes, I started it with a social worker, Alice Scott-Strauss, because there were so many patients being sent to me in private practice who had affective disorders and who needed not only pharmacotherapy, but practical interpersonal, social interventions, rather than the more doctrinaire therapies of the day.

PC: How was it set up? Were you teaching residents in the mood clinic? Where did the patients come from?

HA: All residents rotated in the mood clinic, but many chose it for their entire fourth-year elective. This was a very invigorating experience. As far as patients, some were sent to me, others were screened and recruited from the larger outpatient clinic; eventually many were sending their children. But I want to emphasize that one must see VIPs, including university faculty and their offspring, in private practice because that's how you develop strong relationships which enlightens family members, who are the ones to spread the good word about psychiatry. These were exciting times for psychiatry, which had the full support of the medical school dean and Chancellor at the University of Tennessee Health Sciences. We did conferences, including a major conference on diagnosis; the Vice-Chancellor, Jim Gay, formerly a neurosurgeon from Baltimore - who had been exposed to Adolph Meyer - gave us \$22,000, a lot of money in those days, to stimulate interest in psychiatry. I decided to devote it to an international congress to examine the question whether laboratory tests could be used in the diagnosis of mental disorders.

PC: This was at Memphis?

HA: Yes, 1975, there were 20 national, including Sam Guze, and international speakers, such as Sir Martin Roth, Arvid Carlsson, and 300 attendees. I remember Danny X Freedman saying in his opening remarks that the "biological mafia" had landed in Memphis, an unlikely place for such a conference! Incidentally, we still don't have much in the way of laboratory tests to aid in the diagnosis of the so-called functional mental disorders. This is so, because genes don't recognize the DSM system. The Proceedings of that conference was published in a monograph, *Psychiatric Diagnosis: Exploration of Biological Predictors*, by Spectrum Publications, in New York, in 1978.



PC: So, a lot was going for you in Memphis and you stayed there and began to publish the results of your follow up studies. You used a structured interview, didn't you?

HA: Actually, a semi-structured interview, a modification of the Washington University Diagnostic Interview that Sam Guze was kind enough to provide me during my first "pilgrimage" to St. Louis, but we edited and expanded the parts that had to do with the less than syndromal conditions.

PC: How many patients did you finally end up collecting and publishing on?

HA: The total number that I personally examined and followed up systematically would be about 1,000.

PC: It was all on nosology or diagnostics in follow up?

HA: Treatment, as well. There's something that would interest you. In our mood clinic, there were no suicides. That is a remarkable phenomenon, on which I haven't fully published yet, but was interviewed about on the first page of the *Wall Street Journal* in 1983.

PC: Is it because you were treating them well and following them closely?

HA: I think that was the case, looking at what is essential, the correct diagnosis, rigorous treatment, systematic follow-up and paying attention to the social-interpersonal aspects, rather than the unpractical things from theory-driven schools of psychotherapy. You know what I mean by that?

PC: I do.

HA: One other thing. I was hooked to lithium as a resident from as soon as it was approved for clinical use in 1970. My first manic patient, who received lithium with sodium chloride, as was the custom in those days, was a prostitute, and she made a remarkable turn around. We helped her get off the streets, so I fell in love with lithium. That's one of the reasons I started the mood clinic. She helped other prostitutes get off the street. It was social psychiatry via pharmacotherapy and practical psychotherapy. Someone once asked me to define, what is practical psychotherapy? And I said "that which is not unpractical."

PC: I had the same experience. We had a manic minister, a kind of Elmer Gantry, in the hospital who had 12 or 24 ECT's. Nothing made a difference until George Winokur had the pharmacy make up lithium before it was marketed. The patient got completely well. It was the most remarkable change in behavior I've ever seen and I, too, have been hooked ever since.

HA: One other thing about lithium, we learned that you could use it at doses and blood levels less than what was being officially proposed.

PC: For patients with mania or depression?

HA: Once “stabilized” acutely, during prophylaxis as outpatients, whenever feasible we endeavored to lower the dosage compatible with reasonable “euthymia” - without obliterating all moods - to make sure that they would stay on it. Concurrently you could use something like thioridazine, which was a great agent in those days, to deal with the more “minor” mood swings in either direction, plus psychotic symptoms and mixed states for which thioridazine was crucial.

PC: Those were my two favorites.

HA: It took great clinical skill to persuade the patients to ingest these agents that had so many side effects, which we told them were signs that they were beginning to act on their CNS! Curiously, lithium patients got so much attention, that those who were not deemed to be good candidates for it, felt left out.

PC: Both factors could contribute to their not being a suicide.

HA: Absolutely. They stayed on their dual prescribed agents, we did not label them as “drugs,” while receiving the personal attention regarding their life problems.

PC: Right. Mellaril (thioridazine) was first tested as an antidepressant and did well in comparison to the older antipsychotics. So it was a good agent to use. You published a set of papers from that clinic and, of those manuscripts, what important points do you want to leave us with?

HA: I would say the chapter you invited me to write in the *APA Reviews* volume 2 in 1983, is a good synthetic summary of much of my research papers in the first decade of my academic career. You wanted a review of my ideas on diagnosis and I presented the bipolar spectrum concept, so prevalent in outpatients and the relatives of full-blown manic-depressive patients.

PC: That is the first step in preventive psychiatry.

HA: I completely concur. The spectrum concept has become very important in terms of many things like early diagnosis and treatment and in terms of the genetics and phenotypes. In San Diego, I collaborated with John Kelsoe, and we found the linkage on chromosome 18p for cyclothymia. Once you have a temperament identified, we are closer to the origins of the disease, before it becomes clinically declared. I think it’s important that we study processes which are closer to the normal in our biological investigations.

PC: How did you feel then when they made cyclothymia a diagnosis rather than a temperament?

HA: There was no way of stopping Spitzer and other nosologists in what they were doing. Not to belittle the enormous historic importance of the first DSM-III, but he was borrowing from other

people's work and transmuting data-based criteria as his logic dictated or "votes" of experts suggested. Things have changed very little since then and I don't attach great hopes to DSM-5 either, indeed, I have declined to contribute to it.

PC: Do you think that cyclothymia and hyperthymia should be temperament traits?

HA: Absolutely, including dysthymia. They should not be considered diseases. That's the beauty of the concept of temperament. You can diagnose early, not everyone progresses to a disorder, dysfunction level.

PC: Tell us about that.

HA: Although I had lived in Memphis for a long time, it wasn't until I met Kareen, my future wife in Paris, that I was sensitized to the blues. In those days, many of these singers were more appreciated in Europe, Paris or London. One day, I heard Dr. David Evans, a Memphis ethnomusicologist on the radio say something about having the "blues" in the morning. When I realized that the expert on the "blues" was in Memphis, Kareen Akiskal and I did a formal study with him.

PC: What did you find?

HA: Much of the data remains unpublished. We published a paper in French in *Nervura* in 1994. What we found is that the "blues" temperament is split between cyclothymia and hyperthymia; interestingly, most did not have any mental disorder, unless you counted excessive use of alcohol before performance. There were a lot of suicide attempts in their families associated with cyclothymic probands blues musicians. That's one of the reasons I was asked to deliver the Eli Robbins lecture.

PC: We were all fascinated with it and I'd forgotten the part about suicide. You're saying that people need to have the down part to be suicidal?

HA: Not necessarily. My hypothesis is that it's the sudden change from a relative high to a down mood. That happens in cyclothymia. Hyperthymics may also experience brief, sudden low moods, especially in the later years of their life. Both situations can prove to be dangerous from a suicidality perspective.

PC: Or the opposite? Going from depression to mania as they get more energy?

HA: The sudden downshift, in my experience, is more important. Antidepressants don't do very much for the depressive side, if anything they make it worse. Of related interest, one of the challenges for American psychiatry is to teach not to confuse bipolar with borderline personality.

PC: That's another one of your major contributions, isn't it?

HA: Avoiding the diagnosis of borderline personality in bipolar disorder, which is tautological, I published on that in the *Journal of Clinical Psychiatry* in 1985.

PC: If they're not "borderline," what would you call them?

HA: Cyclothymic. Cyclothymics can be irritable, angry and, obviously, labile, very variable in mood. That's similar to what borderline personality can look like, except that borderline patients by DSM definition also cut and may mutilate themselves.

PC: I had a patient that burned herself.

HA: That's perhaps beyond cyclothymia and even borderline personality. We have developed a temperament scale that helps in evaluating cyclothymia and other temperaments.

PC: Tell us the name of the scale.

HA: TEMPS, Temperament Evaluation of Memphis, Pisa, Paris and San Diego, published in *Journal of Affective Disorders* in 2005. It's being used clinically as well as for research in at least 25 countries worldwide. This is a joint research effort, which started with Kareen Akiskal in the evaluation of affective temperaments in creative artists in Paris and, more recently, worldwide. During the last few years we are also using it in collaboration with John Kelsoe to search for the genes underlying the bipolar spectrum, which, as I am proof-reading this typescript just prior to publication, has led to the tentative identification for several genes corresponding to mania subdivided on the basis of longitudinal patterns of hyperthymic vs irritable temperaments. This is of great relevance to pharmacotherapy as it relates to differential response of mania to lithium vs divalproex.

PC: I want to go back to your history. You were in Memphis for how many years as a resident and faculty member?

HA: Almost 20 years, I was there until I went to NIMH in 1990.

PC: And you were Full Professor?

HA: William Webb, then my Chairman, had proposed me for that rank when I was 33. You were one of the external reviewers of my record of publications and you wrote a letter of reference on my behalf saying that people who did innovative clinical research are good teachers and the Dean had agreed.

PC: So he promoted you.

HA: The Dean was very impressed by your letter, among those of others like Art Prange. You don't become a professor in a clinical department at the age of 33 in most medical schools.

PC: Then you went to NIMH?

HA: Many years later, for four years, 1990-94.

PC: You had a special title didn't you?

HA: Senior Science Advisor to the Director and subsequently you, too, joined in that position.

PC: Right. I only stayed a short time.

HA: The four years I stayed at NIMH marked a partial shift in the Institute from schizophrenia to affective disorders, including education of the public and non-psychiatric physicians about mood and anxiety disorders. I was involved in all that and much more, while being in charge of the Collaborative Depression Study (CDS).

PC: With Dr. Maser?

HA: Yes, Jack provided fantastic logistic support and methodological rigor. Dr. Klerman, the chair of the collaborative study, was very ill during that period, preceding his premature death and asked me to take over the CDS, in the middle of a review session, as two of the external reviewers were challenging the need to continue the prospective follow-up of this landmark study. As this was a cooperative project of NIMH in partnership with five University Centers, the Institute had invested a great deal of resources and funding into it, and therefore, had a vital interest in it. Actually, I was asked to write a 75-page "concept review" for then NIMH director, Fred Goodwin. Those were the public health priorities of the day, at that stage of the art and science of affective disorders. All of this is in the public domain.

PC: I didn't realize that. By that time I had gone to Minnesota. We were starting to do the temperament stuff from the collaborative study, which you continued when you moved to San Diego with Dr. Judd, didn't you?

HA: That's correct.

PC: And you got Dr. Judd involved in outcomes? You did some very important papers together.

HA: That was several years after my leaving NIMH. We examined the "microstructure" of mood disorders. We demonstrated mood disorders to be chronically fluctuating illnesses, not just episodes. That was a fundamental point to make with multiple data points over long periods of prospective observation. Only a carefully characterized large sample like the CDS had prospective data to lend credibility to this conclusion that has led to a paradigm shift on the necessity of

uninterrupted treatment of mood disorders. Bipolar type II hypomania was the only condition in which there were some positive attributes, which is expected, but primarily with very mild hypomania.

PC: Is there something else you would like to mention about your contributions to psychobiology?

HA: Our work in the sleep laboratory in Memphis in the neurophysiology of depression. We studied a young man who was sleeping too much and thought to have narcolepsy or “characterologic depression.” He was actually suffering from a chronic subthreshold depression, as we validated by his having short REM latency, but not SOREMPs. That started a series of studies on shortened REM latency in various conditions. It was largely limited to depression, which, in turn, led to pharmacotherapeutic trials. We did the first open study, published in the *Archives of General Psychiatry* in 1980. It would be impossible to publish something like that in the *Archives* today. There were many replications of our sleep studies in dysthymic and related low grade depressions - at least 10 - showing most classes of antidepressants to be effective in double-blind studies, as a result, millions of people suffering from chronic depressions worldwide have benefited from our research. This research has been recognized by many prestigious prizes and distinctions, such as the NARSAD, the Anna Monika, the Gold Medal of the Society of Biological Psychiatry, the Aristotle Gold Medal and the Jean Delay Prize of the World Psychiatric Association, as well as several honorary doctorate degrees. For me the greater satisfaction is to have brought smiles to the faces of people with chronic depression. It’s personally important for me, because I never saw a smiling face in my family when I was growing up. They were among the rare survivors, after exposure to the first genocide of the 20<sup>th</sup> century during the last years of the Ottoman Empire.

PC: I know you were influential in seeing that people with dysthymia were treated, but I didn’t realize it stemmed from your sleep research - nor did I know its personal significance for you.

HA: If we hadn’t found shortened REM latency, nobody would have believed that seemingly character disorders could represent veritable pharmacotherapy responsive affective conditions. You can use family history and course as external validators, but people will not be impressed because dysthymia doesn’t look like depression. Sufferers look like chronic “complainers” or people with so-called character disorders.

PC: I treated a medical student's mother with depression and after about six weeks she came in and I asked, how do you feel? She said, "better, you moved back my dreaming." That's just what happens, right, when someone gets well?

HA: That we often hear, but it is a far more complex matter, because different classes of antidepressants influence REM and slow wave sleep in varied fashion.

PC: The way patients describe their symptoms confirms what we think we are doing. I enjoy that part of seeing patients and it brings a smile to my face, too.

HA: For 12 years, I was the research director of the sleep laboratory at the Baptist Hospital in Memphis and that was a remarkable experience, because for a psychiatrist to see relatively normal people from a psychiatric perspective is much of the job in a sleep lab. We would examine sleep apnea, hypersomnia and a lot of so-called psychophysiological insomnia - the terminology keeps on changing, though. I interviewed something like 2,200 people, the whole spectrum from the poorest to the most accomplished people in terms of profession, including many famous musicians addicted to drugs. Regrettably, psychiatry lost its chance to have its neurophysiology laboratories. They have been largely appropriated by pulmonology as "rhoncology," snoring clinics, to evaluate sleep apnea.

PC: Don't you think the key to doing good clinical research is seeing a lot of patients?

HA: Absolutely. You become a psychiatrist by seeing patients, not by reading textbooks or making tapes and watching them.

PC: I concur. I will add: Nor by talking to your supervisor.

HA: I always made the student sit next to me when I saw patients. That's how I teach. That's how I supervise.

PC: That's why you've won so many teaching awards. You won them at Memphis and won them in California, including best teacher of the year, right?

HA: One was called "provocative" teaching prize, reflecting how residents felt. I was helping them thinking outside the box.

PC: You went from NIMH to California where you rose to the rank of a Distinguished Professor. Do you have an international title too?

HA: Joint appointment with International Health and Cross-Cultural Medicine. That's part of the Vice-Chancellor's program for International Health. For a decade I taught in seminar format on disasters, especially on community responses to earthquakes. I've had a very rewarding career and

I am grateful. Medicine is all about having great disciples, to transmit our experience and excitement about innovation to be able to better help patients.

PC: There are two other aspects that I want to talk about. More than any other psychiatrist in America, you have an international reputation, partially because you work with so many people in other countries. Have you ever thought about how many countries?

HA: Ten countries in the long-term, and another 20 in the short-term, involving all five continents of the globe.

PC: You really are an international researcher. In most of these countries you work with people on mood disorders. Is that right?

HA: And temperament.

PC: Have there been things that you've learned that you brought to your work here in the States?

HA: This experience has enriched my perspective in many ways; it could fill several volumes! As we are on pharmacotherapy, I would like to mention that I learned from Italians that low doses often work quite well; collaboration with Giulio Perugi has been very rewarding.

PC: You're talking about antidepressants in low doses?

HA: For most medications, also the importance of rational "polypharmacy," again in small doses. My former fellow, the Brazilian Olavo Pinto, is a wizard when it comes to creative combinations of small doses of different agents. International contact is also vital, among others, because of different syndromes in different countries. The Japanese have very interesting syndromes. When I was first invited to Japan in 1992, they said to me, "Professor, living in Memphis, how did you learn about the Japanese personality, and what do you feel about the temperament that is devoted to work and to harmony, and is self-sacrificing and self-effacing, the dominant Japanese personality that underlies the cohesive structure of our society?"

PC: They didn't understand the universality of it?

HA: I guess they live in their own universe. They've got a peculiar, interesting and rich culture. The cohesive nature of their social order is quite unique, I must say.

PC: And, you speak how many languages?

HA: I can say few, brief, polite sentences in many languages, including Japanese. But as far as speaking, it is six.

PC: Which are?



HA: Armenian, of course, and Arabic, and I picked up some Turkish from my family, French and, of course, English. English was my fifth language. Italian, the sixth, I can manage as far as psychiatry, but not much beyond that.

PC: And, you write in how many languages?

HA: At least three.

PC: English and...

HA: French and Armenian. I can fill forms in Arabic.

PC: Are there other things about San Diego I should know or we should have for your history?

HA: Well, it's one of the most important departments in the country and we have almost "everything."

PC: That speaks to Judd's leadership, doesn't it?

HA: He is a master in recruiting talent. He was very patient with me; it took him 12 years to finally get me to move to San Diego. He recruits you to give you two jobs to start with, but you end up doing five or six, even though the salaries at UCSD are relatively low with respect to how expensive the real estate is.

PC: How about your funding?

HA: I've never been funded by NIMH extramural grants, even though I was there for four years.

PC: Don't you think that part of the reason is you collect large samples and that always seems improbable to grant reviewers. They're always concerned that you're overly ambitious.

HA: Ambitious it is, why be in academia if one will do mediocre work? I never listened to the advice to tone down the scope of what I was doing. I said, "no, I can do this and I'll show you what I can do." And I've done just that. I'm one of the most cited researchers in ISI; I've been in the top 10.

PC: One of the top 10 psychiatrists?

HA: Among Psychiatrists and Psychologists.

PC: I want to switch to talk about the *Journal of Affective Disorders* because that's another of your major jobs and contributions, isn't it?

HA: The other day I was making some decisions about manuscripts and I thought this is the best job I ever had. Many people wanted to be editor-in-chief of the *Journal of Affective Disorders*.

PC: When George died?

HA: When he was very ill and someone said go and talk to him. And I said, “no, I’m not going to talk to George, that’s not a noble thing to ask a dying man to appoint me as his successor.” However, I said to the publisher, Elsevier, “if George decides I deserve to be his successor, I will seriously consider it.”

PC: They wanted me to be the editor and I said I wasn’t good at that. I thought they should ask you. You seemed like the logical person.

HA: I’m most appreciative because, it has helped me to not only continue George Winokur’s legacy, and yours at the same time, but also to introduce innovations of my own. I take particular pride in helping young investigators whose name is unknown and help them to get a publishable manuscript.

PC: Is that right?

HA: Yes, even against the reviewers’ negative, sometimes “damning” comments, even though we caution them to avoid such language. Such consternation may sometimes reflect something really innovative at the core of papers by novices in the field. Of course, there must be something salvageable in the submitted manuscript. I then help them over many months to reshape the manuscript.

PC: That’s wonderful.

HA: I have done that from the beginning. Danny Freedman and, to some extent, John Nemiah were my models for introducing young talent. They made their handwritten suggestions on my own manuscripts, when I was young.

PC: How many papers are submitted to the *Journal of Affective Disorders*?

HA: It is a huge number and it is increasing exponentially. That, on the positive side, means the journal is enjoying great popularity because of its scientific rank, broad scope and innovative contributors to our field. Unfortunately, the peer-review system is in crisis, due in part to the proliferation of journals on the Internet with increased burden on the limited pool of reviewers. Often, the editor has to do the review himself if the paper is in his area of expertise. Fortunately mine is rather broad and still I derive particular satisfaction examining in depth, the emerging scientific developments. That means these days I accept some without formal external review; I do many of those reviews myself. North Americans are relatively reluctant to review articles these days, compared with their European counterparts.

PC: So, you’re sending more of your articles to Europeans for review?

HA: I tend to use relatively young researchers or scholars, who are more motivated to enhance their careers, from both continents, but I can sometimes get pretty good reviews from Japan and Latin America and Australia as well.

PC: You usually send it out to two reviewers?

HA: We endeavor to send to three.

PC: And, you get it back from all three?

HA: Rarely. Sometimes we are lucky to get one.

PC: How long have you been doing this?

HA: Since 1996. George Winokur was a no-nonsense editor and his example and practical wisdom of running the Journal on a day-to-day basis guides my overall stewardship of the journal. His infectious laughter, even when facing tough situations is unforgettable.

PC: What about the organization associated with the Journal; do you want to tell us anything about that? Are there other things about international psychiatry that we need to get down on tape? What is ISAD?

HA: The International Society for Affective Disorders. It's for mental health professionals around the Journal interested in getting together and networking. We try to get members initiated into affective disorders by joining. Many young clinical affectiveologists, I believe I have coined this term to refer to our specialty, are part of it and that's the emphasis I want. It's the pleasure of initiating young people into the excitement and elegance of clinical research, because we publish all kinds of articles in the *Journal of Affective Disorders*. It's not only biology or genetics and neurophysiology; we publish clinical follow-up studies, epidemiology, social and cultural aspects, personality and temperament. I think that broad scope is extremely important. We periodically publish sponsored or editor-initiated special issues or supplements, focusing on special topics. I am responsible with this aspect of the Journal, whereas the European Editor, Professor Cornelius Katona from the UK is in charge of Journal logistics and the "political" governance of ISAD. We have had a very cordial relationship since the beginning, on the same wavelength on the major challenges facing the Journal and our broad specialty.

PC: The ISAD used to meet just once a year. Now, are they meeting more often?

HA: Once every two years and then regional meetings, as well. Canadians have been very active in ISAD.

PC: Okay, are there other things we should know about you?

HA: I'm not very much of a political creature. I'm relatively easy to approach, though somewhat shy, except on the stage!

PC: You did do poetry and art; I saw it in your CV.

HA: I would say as a young person, many write poetry, especially when one falls in love.

PC: I don't think that's true, but some people do.

HA: When you fall in love, verses flow, it is like a natural hypomania!

PC: That's funny. I have to tell you another story and I want you to talk a little bit about this before we finish. I had a patient, whom I'm sure you knew, too, who came to me one day and said he didn't want to be a bipolar type II; he wanted to be just a depressive. He resisted any other diagnosis and said "I am a hyperthymic obsessive-compulsive depressive." At that point I had not heard of hyperthymia, but he'd read the literature and the patient said that's what Akiskal has described, and that's what I am. He was right. He was bipolar, but he certainly was hyperthymic, also. When did you come up with that concept, after cyclothymia or at the same time?

HA: In 1976, I decided that the modification I'd made on our earliest outpatient diagnostic interview required something more than DSM-II personality constructs and that histrionic, antisocial and cyclothymic and dysthymic were insufficient to describe the variety of human nature, especially those with high energy and vigor and enterprising. Therefore, I decided to delve further into the German concepts and read Kurt Schneider again. In his opus *Psychopathic Personalities*, he uses the term "hyperthymic psychopath," psychopath in the sense of abnormal personality, purely in a statistical sense, with no moral judgment attached to it. Thereby, "hyperthymic" became part of our questionnaire and later the temperament scale; we operationalized Schneider's descriptive essay in order to quantify it psychometrically. So, these German concepts entered American psychiatry. That's a very good marriage, classical concepts in methodologically-driven American research.

PC: I think the old classical nomenclature and some new biologic evaluations are going to be the key. We're going to extend it to another level, don't you?

HA: I had a Rumanian-origin disciple in San Diego, Robert Bogdan Niculescu, who used to say "in the era of genomics, the phenotype will be king." I think the future is in the creative delineation of phenotypes and not in the largely committee-manufactured DSM-IV nosologic neologisms and constructs, which refer to over 400 ways in which one can lose one's sanity. We should endeavor to define them in their non-pathological versions such as temperaments and related affective and

cognitive biases of responding. They should be detected early and one should endeavor to prevent those from becoming disorders. That's a future perspective and challenge to our field.

PC: I think we want to do one more thing before we end. Tell me again what you mean by mood spectrum disorder. What does it encompass?

HA: Mood spectrum is not my terminology, that's Angst's.

PC: What do you call it?

HA: Bipolar spectrum.

PC: What does it encompass?

HA: I will refer to several entities within the bipolar spectrum to highlight their clinical, pharmacologic and genetic significance. At the top of the hierarchy is schizoaffective, bipolar type; followed by the well-known "dichotomy" of type I bipolar and II; next comes type II and a half, these are cyclothymic. The next level of bipolarity is type III, hypomania, which is associated with medication, or ushered by somatic treatment. It is depression with familial bipolarity and which, in our experience, are not infrequently refractory to most treatments as they have been exposed to multiple antidepressants. We also refer to type IV, which is hyperthymic with or without depression, important because these people can be briefly and suicidally depressed and kill themselves before anybody knows about it as they can't tolerate any depression. The next entity is the type V, the unresolved question of recurrent "unipolar" depressions. They are often early in age at onset, and may originate from familial bipolar background and, we therefore prefer to consider "pseudo-unipolar," especially when more than three major episodes have occurred, and subtle depressive mixed states have developed; in my experience, antidepressants do not do very well with these folks. The last one, type VI, has bipolar-like features, like activation, sexual indiscretions, in the context of dementia. This is important because they often respond to divalproex, but not agents used in Alzheimer's. To summarize, conceptually, the term "spectrum" simply refers to bipolar phenomenology of different degrees, which at one level overlaps with schizophrenia and at the other extreme with dementia. It is an attempt to map out a heterogeneous terrain, which, we have hypothesized, will reveal distinct underlying genetic bases. It doesn't mean that they're all due to the same genes, but there's a spectrum in the phenomenology. Here's the potential heuristic value of this concept. In their "dilute" expression these genes seem to harbor adaptive advantages. We must be very caring towards the mentally ill, not just for humanistic Pinelian reasons based on their being ill, but especially in the case of manic-depressive psychosis,

they're, Kareen Akiskal and I submit, the carriers of genius or the genes of genius. Many are on the border of "insanity," it's an old idea; it goes as far back as Aristotle or perhaps much earlier.

PC: That's wonderful. I think that's a perfect way to end, but I can't quite end here. I just want to do one more thing. Now, we've talked about your contribution to psychiatry, but from a personal standpoint, are your parents alive? Do they appreciate what you've added to the world?

HA: My father, as already mentioned, died in a car accident when I was 16. I was in high school then. My mother died in 1986, so my mother knew something of my work and she was very proud to have given birth to me.

PC: Did she die in Paris?

HA: No, she died in Lebanon. She wanted to go back, because my aunt, her sister, was ill, so she went back and died there, also wanting to be buried next to her husband, my father. She knew about my career. One of my former professors she met in the States had said to her that I was by far the very best they had had, or something to that effect. And that was the best day for her, and for me, too because that professor had always been very critical of me, or at least he came across that way, and my mother to see a union of herself and my father, both genocide survivors, contribute to this noble profession about the intangible mysteries of the human mind and the ways it can go wrong.

PC: Are you an only child?

HA: No, I have a brother and a sister, both older than me.

PC: Where?

HA: My brother, 12 years my senior. He also died in Lebanon.

PC: Your sister is still living?

HA: She lives with her husband in Los Angeles; she is retired from a lifelong career as a librarian.

PC: And, then, about your wife, Kareen?

HA: I owe much to her because when we were college students, she said to me, "you're one of those people who can integrate science and art, and that's the ultimate aim of all human knowledge." I think that she saw something in me and predicted that my career would rise in a meteoric fashion. I don't know how she guessed; we were only 17, enrolled in college.

PC: Then you came to the United States and she was still back in Paris, right?

HA: Yes, I came in 1969.

PC: When did you finally marry?

HA: The Armenian Archbishop of Paris is a close friend of mine from high school. He once said to us, in front of God, a man and a woman are married when a man's eyes fall into the woman's eyes and merge with her soul.

PC: That's beautiful, so you were married then. Is there anything else we should be covering?

HA: I wish to conclude by thanking you for this opportunity to be forced to be narcissistic: You're very kind in your appreciation of the work I've done.

PC: I've appreciated your career from the first time I met you. I think that you've made a major, major contribution to this field and continue to do so. So, thank you.

HA: Thank you. You brought the best out of me.

PC: I loved your summary towards the end, what personal factors motivated you.

HA: Having known you and admired you for many years, I thought that you would be sensitive to it.

PC: Oh, my goodness!

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### **References:**

Akiskal HS. Subaffective disorder, dysthymia, cyclothymia, and bipolar II disorders in the "borderline realm." *Psychiat Clin North America*, 1981;4:25-45.

Akiskal HS. Dysthymia: Psychopathology of proposed chronic depressive subtypes. *Am J Psychiatry*, 1983;140:11-20.

Akiskal HS. The bipolar spectrum. New concepts in classification and diagnosis. In: Grinspoon L, editor. *Psychiatry Update: The American Psychiatric Annual Review*. Washington: American Psychiatric Association; 1983. pp. 271-92.

Akiskal HS, Hirschfeld R, Yerevanian BI. The relationship of personality to affective disorders: a critical review. *Archives of General Psychiatry*, 1983;40:801-10.

Akiskal HS, Maser JD, Zeller P, Endicott J, Coryell W, Keller M, Warshaw M, Clayton P, Goodwin FK. Switching from unipolar to bipolar II. An 11 year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry*, 1995;52:114-23.

Akiskal HS, McKinney WT. Depressive disorders. Towards a unified hypothesis. *Science*, 1978;182:20-5.

Akiskal HS, Pinto O. The evolving bipolar spectrum – Prototypes I, II, III and IV. *Psychiatr Clin North America*, 1999;22:517-34.

Ban TA, series editor. *An Oral History of Neuropsychopharmacology. Volume Seven*. Brentwood: American College of Neuropsychopharmacology; 2011a

Ban TA. Preface. In: Ban TA, series editor. *An Oral History of Neuropsychopharmacology. Volume Seven*. Brentwood: American College of Neuropsychopharmacology; 2011b pp. ix - xxiii.

Blackwell B. Special areas. In: Ban TA, series editor. *An Oral History of Neuropsychopharmacology. Volume Seven*. Brentwood: American College of Neuropsychopharmacology; 2011a.

Blackwell B. Introduction and dramatis personae. In: Ban TA, series editor. *An Oral History of Neuropsychopharmacology. Volume Seven*. Brentwood: American College of Neuropsychopharmacology; 2011b, pp. xlii -lxxxv.

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