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Interviewed by Thomas A. Ban
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Let's start from the very beginning. Could you tell us where and when you were born? If you could say something about your early interests and education.

First, it is an honor to be interviewed for the ACNP archives. I was born in 1949 and brought up in the Bronx. I attended the New York City public schools and, in fact, like many of us in those years had the opportunity to skip the eighth grade. In 1966, I graduated from George Washington High School in New York, which is the high school Rod Carew, the Hall of Fame baseball player attended. I then attended the City College of New York like many of my heroes including Julie Axelrod and one of my key mentors, Morrie Lipton, who I will talk to you about later. After attending the City College of New York, I moved to Boston, where I started working at McLean Hospital in their research laboratories. This facility was obviously much smaller than it is today and I worked as a research assistant in the laboratory of Victor Shashoua who at the time was studying neurochemical changes in the brains of goldfish after a new learning task was accomplished.

How did you get that job?

I obtained that job because I had worked in the Department of Ichthyology at the American Museum of Natural History in New York. I was supported by a small NSF grant during my undergraduate years in New York; this was my first exposure to research. With this experience in ichthyology I got the job, because there weren't very many people that knew how to handle goldfish, I was hired in 1970 as a research assistant at McLean Hospital, a major teaching hospital for the Department of Psychiatry at Harvard Medical School. Once there, I started attending various research seminars. This was a very exciting time, and there were many, many, seminars.

Could you tell us about the people who worked there at the time?

The laboratory was directed by a very dynamic neurochemist, Jordi Folchi-Pi, who had come from Spain to the United States. There were a number of other investigators there, Harvey Shein, a psychiatrist, George Hauser and Joseph Eichman, neurochemists and others. It was a very exciting time and I had the remarkable pleasure of meeting Alfred Pope, the head of neuropathology at McLean Hospital and a professor of pathology at Harvard. He had worked with Oliver Lowry in pioneering microchemical studies of the cerebral cortex. He, in fact, was the person who with Oliver Lowry had invented a quartz microbalance scale so that he could actually weigh each layer of the cortex. And, what Alfred did, in those years, was to dissect each of the layers of the cortex and, then, measure, with very elegant techniques various enzyme activities. This was really the beginning of modern quantitative neurochemistry. Alfred had no children; his wife was a psychiatrist at Massachusetts General Hospital. He took me under his wing and mentored me, almost as a surrogate child. I enrolled into the Master's degree program at Northeastern University, in Boston. It was interesting. I applied to several graduate schools in the Boston area; the chairman of biology at Brandeis University, in Waltham, Massachusetts, said I would never amount

to anything and that I should keep my research technicians job at McLean and not attempt to apply for any higher degree. I remember leaving his office rather crestfallen but Alfred Pope continued to be enthusiastic about my graduate school and medical school training. Alfred Pope served as an adviser for my master's thesis and virtually every day after work we would sit down and use the double-headed microscope in his office and go over the studies that I have been conducting on the blood-brain barrier for my master's thesis at Northeastern. These were studies that demonstrated that during seizures the blood-brain barrier was reversibly opened, allowing proteins and other substances into the brain that normally wouldn't enter the brain. After I finished my master's degree, Alfred said to me, "you must get a PhD, and I think you should get a PhD in neuroscience".

Where did you get your PhD?

There were only three universities in the United States in 1973 that offered neuroscience PhD degrees that I was aware of, the University of Florida in Gainesville, the University of Illinois in Champaign Urbana, and the University of North Carolina at Chapel Hill. Having been brought up in New York City I certainly did not want to live in cold weather. I ultimately ended up deciding to go to Chapel Hill, where I almost immediately met two individuals that would irrevocably change my life: Morrie Lipton and Arthur Prange. Both of these individuals are past presidents of ACNP. The reason I ended up going to Chapel Hill, and not to a program I was accepted into at Duke, in Durham, North Carolina, was primarily because Duke had a double language requirement for the PhD degree and I knew that I would have had difficulty with that requirement.

Could you tell us something about Morrie Lipton?

Morrie was one of the most remarkable individuals I have ever met. He earned his PhD degree in biochemistry from the University of Wisconsin and an MD degree from the University of Chicago. Both he and Art Prange were psychiatrists. One of Morrie's remarkable attributes was that he was as comfortable talking to the fellow that mopped the floor in the research building where we worked as he was talking to the Dean or the President of the University. He was truly egalitarian and that is something that has stuck with me and something that I have tried to emulate. At any rate, I ended up working with Art Prange for my PhD degree.

So you ended up working with Art.

He was my doctoral mentor. My PhD dissertation was on the Effects of Thyrotropin Releasing Hormone (TRH). In those days, neuropeptides were just being discovered in the brain and no one believed that they had effects on the brain, other than endocrine effects mediated by their actions on the pituitary. I remember, time after time, our abstracts documenting CNS effects of peptides submitted to the Endocrine Society for presentation at their annual meeting were routinely turned down for presentation because their leadership did not believe that these peptides were really neurotransmitters. Art Prange was a fabulous role model, because he conducted both basic science research and conducted clinical research, a true translational scientist, and was a fabulous mentor. Part of being a good mentor is to know when students

should be left alone and other times when they need direction; Art was very good at that, and he let me stumble around a bit as I progressed with my PhD studies.

When did you get your PhD?

I completed my PhD in 1976 at the University of North Carolina at Chapel Hill, applied for and awarded a Fellowship stipend from the National Institute of Neurological Disorders and started to work in the laboratory of an internist-neuroscientist in order to begin to learn, molecular neurobiology was then an emerging area. My postdoctoral mentor was Steve Kizer who had trained at NIMH with Julie Axelrod and Mike Brownstein. I spent a year working with Steve and I learned several things. First, it taught me that I didn't do well in a laboratory that had no windows and it taught me that I missed interacting with a large number of students and fellows.

With Morrie Lipton and Art Prange's encouragement, I ended up applying for admission to the UNC medical school and I began as a medical student in 1977. I graduated from medical school in 1981 and, then, began my internship and residency at UNC where I met Dwight Evans, who is a member of the ACNP. Dwight, at the time, was a junior attending on the inpatient psychiatric service at UNC. Over the next four years we probably published ten to fifteen papers together, largely studies of pituitary-adrenal and pituitary-thyroid axis abnormalities in patients with mood disorders.

Didn't you work at Duke at a certain point in time?

I was recruited to Duke University Medical Center with my colleague, Garth Bissette. This was an exciting time in neuroscience and psychiatry. Ranga Krishnan, Saul Schanberg, Ted Slokin and Redford Williams were there, as was Clinton Kilts. I had a variety of graduate students in pharmacology who conducted their PhD research in my laboratory including Mike Owens, who is a member of the ACNP, and Beth Levant, a faculty member at the University of Kansas, and a variety of other fellows and students. We stayed at Duke from 1983 to 1991, and during those years our laboratory focused largely on neurotensin, a thirteen amino acid-containing peptide that appears to be involved in the mechanism of action of antipsychotic drugs. We also began study of corticotropin-releasing factor (CRF), which was discovered in 1981. This forty-one amino acid-containing peptide that controls the pituitary-adrenal axis appears to be hypersecreted in depression and perhaps in certain anxiety disorders; CRF receptor antagonists are a novel class of antidepressants and anxiolytics that are currently being developed.

When did you move to Atlanta?

In 1991, a remarkable opportunity arose that was simply too exciting to pass up and that was the opportunity to relocate to Atlanta to Emory University where the Chairman of the Department of Psychiatry, Jeffrey Houpt, had become the Dean of the School of Medicine. With the sizeable development package provided to me by the university, we were able to recruit a number of talented new faculty, many in collaboration with other departments. These included Michael Davis from Yale, a leading behavioral neuroscientist, Clinton Kilts from Duke, a PET imager and extraordinary analytic neurochemist and Tom Insel from the NIH, who became Director of the Yerkes Primate

Center and, then, eventually the Head of the NSF-funded Center of Behavioral of Neuroscience. Jay Weiss, one of the leading investigators in animal models of depression, joined the department as did Michael J. Owens, my former graduate student and fellow, William McDonald, one of the leading investigators of ECT and now transcranial magnetic stimulation and head of medical student education, and Paul Plotsky from the Salk Institute. We have gone on to continue to recruit young MD/PhD's and MD's and in the almost nine years that I have been at Emory the department has grown considerably in terms of its research portfolio. We have been able to receive generous support from philanthropic sources and substantially increase our NIH funding.

What are you working on now?

In recent years, I have focused largely on the long term neurobiological consequences of early trauma. As I am sure you know, we have an unacceptably high rate of child abuse and neglect, not only in the United States, but worldwide. We have also been conducting studies in laboratory animals, rodents and non human primates, as well as clinical studies, showing very long term consequences of maternal neglect. We believe that the consequences, which are changes in the activity of the HPA axis, changes in CRF gene expression and changes in a variety of other neurotransmitter systems, underlie the vulnerability of these individuals to the development of mood and anxiety disorders. We are now beginning several treatment studies in this clinical population and my hope is that eventually we can begin to look at prophylactic treatment to prevent depression in this "at risk" group.

When I look back at the career that I have had, I have been lucky. I have been fortunate to have a fabulous family. I have had a fabulous team of colleagues, support staff, junior faculty and, perhaps, most importantly in relationship to this current interview is the remarkable friendships that I have made with ACNP members. These individuals, just to name a few, include Jack Gorman, Ned Kalin, David Rubinow, John Newcomer, Jeffrey Lieberman, Peter Kalicas, Dennis Charney, Marty Keller, Danny Weinberge, Dwight Evans, and Alan Schatzberg. They have become best friends to me and my family because we all travel a great deal to a variety of meetings. This is one reason why the American College of Neuropsychopharmacology isn't just a professional society like the American Medical Association or the American Psychiatric Association. In contrast, the ACNP is a college, meaning that the individuals are collegial, and I could probably name twenty or thirty individuals, who I feel sufficiently close to in this college, that I could go to with any personal or professional problem that might arise, either, in my department or in my personal life. And, I believe that's why the ACNP means so much, to so many of us. Of all the organizations I belong to, and I have multiple affiliations with a variety of organizations, this is the organization I feel closest to, and I know that my colleagues would echo these sentiments as well. I was an ACNP travel awardee and became a member, though my membership application was rejected the first time I applied, a not unusual occurrence, as you know. Eventually I became a fellow, a member of the council and was elected president. The ACNP is very important to me. And, not only have my relationships with members blossomed, but with their spouses and children as well. In life it is not only the good work that we do, which

hopefully translate into better care of the patients that we have spent so much time caring for over time, but, also the friendships we have, which, in fact, contributes a great deal to the quality of our lives. It is for that reason that so many individuals have put so much time and effort, without remuneration, into this college. We have lived through fabulous times here at the college and we witnessed tragedies. Morrie Lipton, one of my mentors, suffered a CVA at an ACNP meeting in Puerto Rico several years ago. I think of the ACNP, as a family, usually functional, but occasionally dysfunctional, with occasional squabbles among its members, as one would expect from a talented, intelligent and strong-willed group of family members. There isn't any other organization that combines excellence in neuroscience, clinical psychopharmacology; epidemiology, genetics, molecular neurobiology and brain imaging that this college does. It suits my needs because I can come to these meetings and learn about areas that I simply don't know enough about, and try to take my own research to the next level. I don't know any other organization like this.

Could I ask you a couple of questions about the research you are involved with in developing new drugs?

By history, the development of new agents to treat major psychiatric illness has been an area that largely has been characterized as serendipitous. There have been many attempts at rational discovery in psychopharmacology, but in the end, most of the drugs that we have were truly serendipitous discoveries, including antipsychotics, monoamine oxidase inhibitors and even the tricyclic antidepressants. Because of the elegant work of many members of the college that showed hyperactivity of the HPA axis in depression, the discovery of CRF in 1981, led to a series of studies to characterize whether CRF is, in fact, hypersecreted in depression. These studies, virtually unanimously, pointed to hypersecretion of CRF in depression and, not only that, but our and others' laboratory animal studies showed that when CRF was injected into the brains of these animals it produced the full constellation of what we see in patients with depression and certain anxiety disorders including decreased libido, decreased appetite, and disrupted sleep. This work led to the development of CRF receptor antagonists as potential novel antidepressants and anxiolytics. Several pharmaceutical companies have, in fact, developed antagonists to the CRF1 receptor that preclinically exhibit antidepressant and anxiolytic effects. The race is on to determine which company will be the first to demonstrate efficacy in clinical trials. If efficacy is demonstrated for CRF1 receptor antagonists, then this will represent a new class of agent with a totally novel mechanism of action that may exhibit a broad spectrum of therapeutic activity ranging from post-traumatic stress disorder to major depression to a variety of other disorders, such as irritable bowel syndrome. These agents could even be used preoperatively instead of benzodiazepines to reduce anxiety. The other area that I would want to mention, in terms of drug development, is our work on neurotensin, a CNS neuropeptide that in part mediates the effects of antipsychotic drugs. Basically, what we have discovered is that typical antipsychotic drugs increase neurotensin gene expression and release in the striatum and that appears to predict extrapyramidal side effect liability whereas atypical antipsychotics, the latter including olanzapine, risperidone, and quetiapine increase neurotensin gene expression in the nucleus accumbens, but not in the striatum, and this predicts the clinical efficacy of antipsychotics. The question as to whether a

neurotensin receptor agonist might represent a novel class of antipsychotic drug is a very hot avenue of investigation at the current time. No such molecules have yet been discovered.

Simultaneously with your research you have built a very successful department of psychiatry. So, you have administrative, teaching and clinical responsibilities. It has to be a difficult task to deal with all the different responsibilities.

I suppose so. We have about 110 faculty members in the Department of Psychiatry at Emory. Of all the departments at Emory, we are the second best funded department in terms of research. Obviously, a considerable administrative load is associated with running a large department. I have been blessed to have vice chairs that I clearly have to depend on and to whom I delegate tremendous responsibility. Steve Levy, the Chief of Psychiatry at Grady Hospital, is the Vice Chair for Academic and Clinical Affairs and Clinton Kilts, is the Vice-Chair for Research. Because I have a fabulous staff as well as these vice chairs, I have been able to continue my research career and teaching as well. I currently have 3 MD/PhD students that I am mentoring, as well as a number of Fellows. I have a fair number of patients that I still follow, approximately eight to ten hours a week, largely with refractory mood disorders. Then, of course, I have the inevitable administrative responsibilities, including search committees, chair's meetings and the like. Recently I have had an increase in my interactions with the Carter Center, which is also part of Emory, and Mrs. Carter, of course, has a special interest in mental health. I would conclude by saying that one has to love these jobs in order to do them even reasonably well. I would never suggest that I was very good at all of these tasks but I can tell you that I have enjoyed them. You really have to love your faculty if you are willing to take on the often thankless task of the administrative responsibilities which enable the faculty to be successful. I think the job of the chair of the department is to work as quietly behind the scenes as possible in order to maximize the opportunities for the faculty to accomplish their goals; their clinical goals, their research goals and their teaching goals. If you can do that, without them knowing how precarious this house of cards is sometimes, then, I think you have accomplished your job. I have been very lucky in my life to have the support of great mentors and great students and great colleagues and a great family and would simply hope that all of you watching this video could be as lucky as I have been in the fifty years I have been on this earth and, hopefully, a little bit longer.

During the years you have written many papers. Could you tell us something about your publications?

I have published 600 peer reviewed journal articles, including reviews, many co-authored by my colleagues and junior faculty. The journals in which they are published range from the *Journal of Neuroscience* to *Science*, *Nature*, *Biological Psychiatry*, *Neuropsychopharmacology*, *Journal of Clinical Investigation* and the *Proceedings of the National Academy of Sciences*. I have also had the pleasure of editing the *Textbook of Psychopharmacology* with Alan Schatzberg, currently president elect of ACNP and one of my closest friends. This week the book that we authored together on psychopharmacology for non-psychiatrists, largely for primary care physicians, is, about to be published. I have also edited about 12 other books in the areas of neuropeptides,

neuroendocrinology, and psychoendocrinology. I think of all of my publications, the *Textbook of Psychopharmacology* is, by far, my favorite, because it has performed a service for the field. This year, I will complete a four-volume *Encyclopedia of Psychology and Neuroscience* that Ed Craighead, a professor of psychology at the University of Colorado, and I are co-editing. This is formerly *Corsini's Encyclopedia* used largely by psychologists, which we have converted to an encyclopedia of psychology and neuroscience. I am also now working on a CD-ROM project on neuroscience in psychopharmacology for psychiatrists and other physicians, which I hope will be used as a teaching tool to educate about receptors, receptor subtypes, transporters, molecular biology, circuits and cognate areas. I also write a column for the journal *CNS Spectrum* every other month on a topic of my choice, which has ranged from personal columns about tragedies in our lives to topics of professional interest. .

During the years you served on many advisory boards.

Yes. I have served on a number of advisory boards in mood disorders and in schizophrenia. I have worked very hard to try to bring together the pharmaceutical companies and academic investigators to discuss investigations of novel clinical agents, and ethical concerns, such as placebo use in severe psychiatric disorders. I am currently the chair of the Scientific Advisory Board of the National Depressive and Manic Depressive Disorders Association, an advocacy group for patients with bipolar disorder and depression. I am the vice chair of the scientific advisory board of the Anxiety Disorders Association of America, led by Jerilyn Ross, a remarkable individual. Dennis Charney is currently the chair and I have worked closely with him in that organization. I have been involved with the National Alliance of the Mentally Ill (NAMI) and with the Mental Health Association. I serve on a foundation board in Atlanta dedicated to the treatment of patients with mental illness, the George West Mental Health Foundation.

What would you consider your most important contributions?

I think I am probably as good a fisherman as anyone in the college and have tried to convert many ACNP members to fly fishermen. I'd rather be fly-fishing than probably doing anything else except for being with my family. Scientifically, the contributions we have made in the CRF field and the neuropeptide field in general, and, perhaps, some of our work in the serotonin transporter field will stand the test of time.

You have trained many people. Would you like to mention some of them

I have had the chance of working with many superb junior colleagues. Beth Levant was my PhD student, one of the world's experts on the D₃ receptor, and she is on the faculty of the Department of Pharmacology at the University of Kansas. Mike Owens, my first PhD student is on the faculty at Emory, and has gone on to conduct remarkable work on urocortin, the CRF2 receptor and their role in the mechanism of action of benzodiazepines. Jeff Newport, my former Fellow, is now a faculty member at Emory working with Zachary Stowe, another former fellow on depression in pregnancy and in the puerperium. My junior colleagues have been absolutely terrific in contributing to my own work and then moving on to establish their own independent careers.

So you trained quite a number of people who pursue now independently their own area of research, and you have yourself opened up several new areas of research that will hopefully grow.

Well, as you know, Tom, different scientists have different styles. Some work on one distinct area throughout their entire career. Others, like myself, prefer to conduct research, make new findings and then move on to other areas. Having diverse interests has really kept me going.