ALFRED J. LEWY

Interviewed by John M. Davis
San Juan, Puerto Rico, December 11, 2006

JD: This will be an interview with Alfred Lewy.* It is December 2006. I'm John Davis. What sort of training did you have in Psychopharmacology?

AL: In addition to getting a medical degree, and, of course, I went on to become a psychiatrist; I also got a PhD in psychopharmacology under Lewis Seiden. He was a great role model in a number of ways. One of the things I liked best about him was his sense of humor. It's very important when you're picking a dissertation advisor to choose somebody who is a nice person, who you can get along with and who is supportive, and Lew Seiden was all of those for me. My dissertation was published in *Science* in 1972. Next, I did my internship and psychiatric residency at Mt Zion Hospital. I then came to the NIMH where I got further psychiatric residency and research training. It's the perfect place to be trained as a clinical researcher. I became interested in circadian rhythms, because I took care of a ward of manic-depressives. Ahead of me in the program was Tom Wehr, who became my next mentor along with his mentor, Fred Goodwin. They were following up on some ideas that the biological clock was possibly involved in timing of manic and depressive episodes. I'd worked there for about a year hoping to make an original contribution to this area, and I thought a melatonin assay would be important. I had become interested in melatonin in mid-1976 when Julius Axelrod gave his Nobel Laureate lecture at the NIH auditorium on a day when I was stuck on the ward taking care of patients, so I couldn't attend. But Tom and Phil Gold, who were a little ahead of me in the program, both attended this lecture. Between the two of them, they were able to recite it to me, almost verbatim. I don't know whether I was more impressed by the lecture itself, or by their ability to remember it so well. In any event, I was impressed, so decided to work on melatonin. In my literature search I found there wasn't a good way to measure melatonin in humans, so that was my first task. Because I had worked in Lew Seiden's lab I knew some biochemistry. Together with S. P. Markey I developed what became "the gold standard" assay for measuring melatonin in humans. It was published in *Science* in 1978. For the last ten years, we haven't used it much but it has led to the development of very good radioimmunoassays. Now there are a lot of people measuring melatonin in research laboratories. Measuring melatonin will probably become a clinical test soon. I remember calling my father

* Alfred J. Lewy was born in Chicago, Illinois in 1945.

when I was in the mass-spectrometry laboratory. I was injecting samples into the gas-chromatograph column, watching the chart recorder pen move while the melatonin was coming through. I remember saying to him, "I feel like I've just put the finishing touches on a rocket ship that's going to take me into the unknown. I don't know where it's going to take me, but I'm sure it's going to take me some place very interesting". He said, "Well, let's celebrate. Your godfather has just been named the Governor General of Australia. Let's go experience the Vice Regal life". We went there for two weeks. When I returned to Washington, DC, I measured my jet lag by measuring my melatonin levels each day at 9 a.m. To my surprise, my levels in the morning were very low. They should have been high, because that was the Australian night, and it should have taken several days for them to come down as my body clock adjusted. I figured maybe sunlight was suppressing my melatonin production, so with Tom, Fred, S.P. Markey and David Newsome, in 1980 we published in *Science* a paper that showed bright light, like sunlight, can suppress human melatonin production. This paper had a number of important implications that I, and others, have been following for the last twenty-six years. One was that you might be able to use bright light to manipulate biological rhythms in humans as bright light therapy. This thinking led to our discovery of seasonal affective disorder (SAD) and bright light therapy, which is now the treatment of choice for SAD. Another implication from our 1980 paper was that blind people had another form of light deprivation resulting in abnormal circadian rhythms. This implication, along with the work I did with Bob Sack, led to the development of melatonin as the treatment of choice for abnormal circadian rhythms in blind people. That paper in *Science* led to two different treatments, bright light and melatonin, for two different disorders that really weren't known before 1980.

JD: I just want to be sure; seasonal depression had not been described before?

AL: Tom later found case reports in the literature describing depression in the winter but we were not aware of them at the time of our entry into this area.

JD: Yes, many things have historical precursors. So, you discovered a disease and its treatment?

AL: I discovered the treatment, and then I looked for a disease to apply this treatment to.

JD: That's an interesting twist on it. You discovered a biologic mechanism.

AL: I figured out two types of circadian disorders that might be related to light deprivation, SAD and total blindness. The discovery of SAD was very serendipitous; a patient, Herb Kern, called me in 1979, who had

read about my work on melatonin, and told me he got depressed every winter. He had been to five other eminent psychiatrists up and down the east coast who refused to treat him, because they didn't think there was such a thing as winter depression. Apparently, they weren't aware of the past literature, either. I invited him to come to the NIH. He had requested I measure his melatonin levels, since he thought he had some atavistic response similar to the reproductive cycles of mammals where melatonin is involved in seasonal rhythms. Instead, I told him we had just discovered that bright light could suppress melatonin. I said, "Maybe bright light can do something to your seasonal rhythm," and he became the first patient treated with light for winter depression, which started the field. If it wasn't for Herb Kern, I don't know if we would have discovered seasonal affective disorder or light therapy. Light therapy is now the treatment of choice for winter depression.

The other two important implications from the 1980 *Science* paper were that melatonin was probably a very good way of measuring biological timing, but that you had to reduce the light levels to get it accurately measured. That led to what is now the standard marker for biological timing in humans. It is called the dim light melatonin onset (DLMO). And, it should be a widely available clinical test by 2011-2012. It will hopefully be a standard clinical test, perhaps with insurance reimbursement. These were the major implications of the 1980 *Science* paper. Melatonin treatment, especially as the treatment of choice for blind people, also resulted from that paper.

JD: Was it recognized, at the time, that blind people had a problem?

AL: In general, no, although, now it seems so obvious. You can go back into the literature and find some hints here and there, but in those days scientists thought that social cues were predominant for humans so it didn't matter if a blind person didn't have light perception, because they were exposed to the same social cues as everyone else. This is why it wasn't thought blind people would have any rhythm abnormalities. I did work with Bob Sack on blind people, giving them melatonin, which reached an important point in 2000 when we published a paper in *New England Journal of Medicine*; Bob was the lead author.

For the light treatment of winter depression, an important year was 1998, when our group and two others published papers in the *Archives of General Psychiatry* on morning light being more effective than evening light, and that supported our circadian rhythm hypothesis for winter depression, published in *Science* in 1987; this paper was entitled "*Antidepressant and Circadian Phase-Shifting Effects of Light".* Then, just last year, we published a paper in the *Proceedings in the National*

Academy of Sciences, "*The Circadian Basis of Winter Depression".* This was based on our discovery in 1992 that melatonin is a chemical darkness signal for the human biological clock. In treating winter depression, we found, just as morning is the best time to give light exposure, afternoon is the best time to administer melatonin, at least for most patients with SAD. Our paper provided proof of the phase shift hypothesis (PSH) for winter depression. So, we now have two phase-shifting tools, light and melatonin, which make up the biological mechanism. Now the question is: what disorders could they benefit? I don't think that schizophrenia is a biological rhythm disorder, but it might have a circadian component. Certainly other types of depression and sleep disorders could have circadian components.

JD: And, also, mania?

AL: Yes, mania. I'm hoping in the next few years we'll be seeing a lot of work using the DLMO to assess bright light and exogenous melatonin's therapeutic efficacy for a variety of psychiatric disorders, especially affective disorders.

I think the last thing I might mention today, unless you have some other questions, is an unexpected finding. I wouldn't necessarily call it serendipity, but it certainly is an interesting finding. When we began to study blind people more intensely, we found that non-photic social cues may be important in humans after all. This idea stems initially from the received wisdom in 1979 that social cues were the predominant time cue in humans. In order to test whether social cues affect human circadian rhythms, we had to study people who didn't have exposure to the light/dark cycle, that is, blind people. They offer a unique experiment of nature, controlling for the confounding effect of light, so that we can see is what else the human clock might be responding to. When we studied these blind people very carefully, we found that they don't drift at the same rate each day. If you're free-running at the same rate each day, it means you're impervious to any other time cues, but if your rhythms are speeding up on some days and slowing down on other days, then some environmental time cue is affecting them.

JD: Free-running would be like if you put a person in a cave, away from all light clues for many days or weeks, their rhythm seeks its natural course?

AL: Right. The natural rhythm is around 24½ hours. It's usually longer than the 24-hour day, so you drift later each day. But, blind people don't drift the exact same amount each day. When the melatonin onset is moving across the day, they drift fast, and when it's moving across the night, they drift slower. So, other time cues, possibly social cues, are speeding up the clock as it's drifting across the day and slowing the clock as it's drifting across the night. We published that in 2005. Jon Emens was the lead author on that paper. We figured out that the speeding up and slowing down response can be quantified and is a direct proportional measure of the sensitivity to social cues. And, we found a robust gender difference. Guess which gender is more sensitive to social cues? Women, of course, because men are from Mars and women are from Venus!

JD: Yeah!

AL: So, women have twice the response to social cues. Free-running blind women seem to have twice the response to social cues as males and they're so sensitive we found that about twenty-five percent of women are entrained to the social cues, so not all totally blind people free-run. Out of twenty-five males, we've yet to find one male who is entrained. This is a very robust gender difference. It seems to start at puberty. In fact, before puberty, in this very preliminary study, all five of our pre-pubertal boys were so sensitive to the social cues that they were entrained to them. It's as if little boys have to be on extra good behaviour to get along with their siblings and parents, because once testosterone mucks up their brains, they become less sensitive to social cues, like adult males. Alternatively, the rigid routine of childhood may be why younger blind people tend to be entrained; once they leave school, more of them start to free-run. In any event, we're now going to follow up to see if we can identify a third type of a time cue for the human biological clock, which might be a social cue.

JD: It's interesting there was a level of serendipity, but some treatments are discovered by chance by clinicians, and it may be many years later the mechanism is understood. But, in this case, you were dually trained, but you hit the mechanism first and, then, found the disease, or maybe I should say you found the diseases.

AL: That's right. A lot of our work grew out of the animal scientific literature and applying it to humans. It's a little tricky, because humans are different than animals even in their biology so you have to know when to generalize and when not to generalize, and that's a bit of guesswork. But, it was basically an obsessive and tenacious focus on melatonin in all of its circadian rhythm possibilities that led to the work I've done over the years. Incidentally, I've been involved in many instances of "reverse translation" where our work with humans stimulates neuroscience studies in animals.

JD: But, you got hooked at NIH on rhythms.

AL: And, melatonin.

JD: You were inspired by a lecture that you didn't hear but that was described to you.

AL: Right. And, I never knew whether or not melatonin was going to lead anywhere, but happily it led to a lot of interesting things. I've done a lot of light therapy studies and a lot of winter depression studies, but I've always returned to my focus on melatonin, and that brought me to other new applications for the blind people, jet lag treatments and treatments for shift work maladaptation, and certain kinds of sleep disorders, advanced or delayed sleep phase syndrome. All those can now be treated with light or melatonin, except light can't treat blindness.

JD: In terms of the diagnosis for winter depression, you were mentioning something about how you might expand on that?

AL: We have a tool, the DLMO, to determine whether the type of winter depression you have is the typically phased-delayed type with the later dawn in winter, or the phase-advanced type with the earlier dusk of winter, the atypical type of winter depression. Depending on which direction your body clock is shifted you need the light, either in the morning as most SAD patients, or in the evening for the atypical subgroup. It's the same with melatonin, although it is given at times opposite to light, since we have discovered that melatonin is a chemical darkness signal.

JD: How did you get onto that?

AL: Immediately after my colleagues and I discovered winter depression and light therapy, we did think it was a seasonal rhythm, and you should use the light, both in the morning and in the evening to change day length. That is how we treated Herb Kern the first patient, but when I came to Portland, I began to wonder if that was a fruitful approach, because humans don't really have a lot of seasonal rhythms. We certainly don't have seasonal reproductive cycles; we have the menstrual cycle. However, we do have a lot of twenty-four hour (circadian) rhythms and there was a theory for non-seasonal depression, a diagnostic concept that Tom Wehr, Dan Kripke and some others developed whereby they thought there was internal misalignment between the temperature rhythm and the sleep-wake cycle, like jet lag. It was a mismatch in circadian rhythms, and I guessed that was going on with SAD and it seems that's the case. Now, if there's a mismatch between circadian rhythms, there are logically two types of ways that mismatch can occur. Your body clock can be phase advanced with respect to the sleep-wake cycle or it can be phased delayed with respect to the sleep/wake cycle. I needed to think this through.

JD: To think it through?

AL: Yes. It's important to think through what the implications are of any thought you have. To try to take it to the next step. It's also important to challenge your own fundamental assumptions and I do this frequently. Being your own worst critic is crucial since you know your strengths and your weaknesses better than anyone else. You know the work of your lab better than anyone else. You know its potential pitfalls, so being your own worst critic is very helpful.

JD: Do you try to be your own worst critic in some regular way?

AL: Not so much regular, as often. So, the future work is now going to be devoted to identifying the social cues that might affect sighted people, as well as blind people, but I've still postponed the final question I've always wanted to answer, which is, what is the function of melatonin in humans? We know it's a good marker for the biological clock. We know we can give melatonin to shift the biological clock and to treat biological clock disorders, but what is the function of endogenous melatonin production? I think that is going to be related to the births of my two boys, which occurred in 2003 and 2006. The theory I'm going to try to test in the next few years is that the function of endogenous melatonin production is for the pregnant woman, through her blood melatonin levels, to communicate biological time to the third trimester fetus and then the nursing mother, through melatonin in her breast milk, to communicate biological time to the nursing infant, until the infant is about 3 months old, when the retino-hypothalamic tract starts to function and the infant can entrain to the light/dark cycle. Before that, they're like a little blind person. They can see, but they can't entrain to the light/dark cycle. I'm sure you know many similar stories of people who are new parents. Whenever I mention to somebody that I'm a recent dad, they always ask, "How's your sleep?" It may be that we can use melatonin to help infants sleep, so that their moms get more sleep and can be better moms. That'll be a new area I'll be working on in the next few years. Perhaps melatonin from the mother is important for optimal early development in her offspring: I call this the maternal ontogenic melatonin (MOM) hypothesis for the function of melatonin in humans.

JD: How would you fit in the melatonin story in an evolutionary sense about how rhythms develop? You mentioned several: seasonal rhythms, 24-hour rhythms, possibly, menstrual cycle rhythms.

AL: Well, melatonin has always been the chemical darkness signal, even in unicellular organisms, for many, many millions of years. A seasonal breeder will use this chemical darkness signal to time seasonal rhythms, but if you're not a seasonal breeder, melatonin is more likely going to be used to time 24-hour rhythms. I think humans have retained the melatonin rhythm and the suppressant effect of light on melatonin, because melatonin does have a function in humans, which may have been disrupted over the last million years, since the invention of fire, because levels in breast milk, for example, are lower in light exposure and the

only way that it could really be high enough to affect the suckling infant would be if there was no light exposure at night. There are some other factors that need to be thought through. In any event, with high definition TV emitting bright light, and if mothers are watching TV at night and suppressing their melatonin, they're probably not getting enough melatonin into their breast milk for the infant to be much affected by it. So, we might think of artificial light as an uncontrolled experiment on our human biology. Perhaps another implication of our 1980 *Science* paper is that it got people thinking about the difference between sunlight and indoor light. As an example, architects are now building houses with more sunlight coming through the windows.

JD: Is there anything we haven't covered that we should?

AL: There are probably a few disorders out there that could be treated with melatonin that may be serendipitously discovered. For example, if you have a lot of people taking melatonin and an astute clinician notices the difference in some disease, that's another condition that is possibly benefited by melatonin. That's not in my approach thus far, but I might start trying to figure out if there is some other use of melatonin, one that may not even relate to circadian rhythms.

JD: Is everything explained clearly enough so that it would be obvious to a layman, because a tape like this could be edited and they could pick something out and put it back where it belongs?

AL: Is there anything more I can do to explain this to the layman?

JD: Did we explain it clearly? And, I know that you want to define free-running.

AL: Before I do, I just want to add to that last thought about the medical uses of melatonin. My guess is a lot of people are going to be taking melatonin because it's safe. There are no toxic side effects, especially at the low doses we have found it effective.

JD: And, that would be?

AL: 0.5 milligrams. We've entrained some blind people to 10 micrograms, a very low physiological dose.

JD: And, in what dose is it marketed now?

AL: Most people are taking 3 milligrams at bedtime.

JD: And, some may be taking higher doses?

AL: Yes.

JD: Sometimes 10?

AL: Yes.

JD: Is there anything wrong with, say, 10?

AL: It won't hurt you, although it may not be any more effective than 3mg for helping sleep. Actually about 30 percent of the population gets sleepy on

melatonin, so they use it for bedtime sleep. We can't predict who these people are in advance.

JD: Does it hang around long enough so it may be too much?

AL: If it hangs around too long it won't shift the clock very well. Low doses seem to work better for clock shifting, because they are more discreet time signals. That's another point that probably should be mentioned. A few people report feeling "hungover" after taking high doses at bedtime.

JD: And, there's a significant difference between, say, 0.3 and 3.0.

AL: That's a ten-fold difference.

JD: And, that's something people need to know.

AL: So, low doses of melatonin may work better than high doses for phase shifting. Melatonin is a chemical darkness signal. It works opposite to light. The way you shift the body clock earlier is to give morning light or melatonin in the afternoon or evening. The way you shift the body clock later is to give evening light or melatonin in the morning. Between these two regimens we've described over the years, you can shift the body clock in either direction and correct either type of body clock disturbance.

JD: I'm just picking the things we may have omitted. Describe what Seasonal Affective Disease is.

AL: Seasonal Affective Disorders is quite common. For some reason, it occurs more in females. The further away from the equator you live, the more likely you're going to have it. It has some of the characteristics of depression, but there is increased appetite, weight gain, preference for carbohydrates, increased sleep and fatigue, despite the increased sleep.

JD: Laymen may still not understand what seasonal depression is.

AL: It's similar to non-seasonal depression, in that you feel sad, hopeless and helpless. There's social withdrawal but rarely thoughts of suicide. There is indifference to things that normally give you pleasure. But sleep disturbance in winter depression is different than in non-seasonal depression. In non-seasonal depression there is often early morning awaking. In winter depression, people want to sleep all the time, which is why we first thought it was some kind of atavistic form of hibernation, but I discarded that idea when I adopted the circadian rhythm theory.

JD: So, it's different from typical depression in that they are sleeping more?

AL: And eating more.

JD: Sleeping more, eating more.

AL: With non-seasonal depression, there's generally a lack of appetite and weight loss. Bipolar depression seems to be similar to winter depression. And, like bipolar depression and some forms of unipolar depression, it's recurrent. That's another hallmark of winter depression. It recurs every winter.

JD: And, what are the behavioural consequences in blind people of not having a rhythm?
AL: When a blind person's rhythms have drifted 12 hours out-of-phase with their sleep/wake cycle, they're sleepy during the day, they can't sleep at night and they're depressed.
JD: They can't sleep at night and they're depressed?
AL: Yes.
JD: I mean their quality of life is adversely affected?
AL: Absolutely.
JD: And, you discovered the disease?
AL: We discovered that melatonin rhythms are abnormal in blind people and when they're most abnormal they're very symptomatic and this is their worst burden, second only to not being able to see. Fortunately we can treat virtually one hundred percent of them with a tiny dose of melatonin, taken every day.
JD: It's a fascinating story. You discovered several diseases and it's interesting from the point of view that you were a clinician and a basic scientist. You discovered a mechanism and, because you were a clinician you went on to discover a disease. It's also interesting that a patient with the disease came to you and you both discovered the disease.
AL: I think that being a clinician and being a scientist were helpful in allowing me to do what I've done.
JD: And, having a setting like the clinical center.
AL: Yes, my experiences at the NIMH were indispensable.
JD: Yes.
AL: And working with great people (there and here in Oregon), particularly with Bob Sack for twenty years.
JD: Let's think for a moment if anything we've missed.
AL: I think we've covered it.
JD: OK, great.
AL: Thanks.

HERBERT Y. MELTZER

Interviewed by Stephen H. Koslow
San Juan, Puerto Rico, December 10, 1996

SK: Today we have a great opportunity to meet with Herb Meltzer* and talk about his extensive and successful career in Psychopharmacology. He is a leading member and past president of the ACNP. He is currently at Vanderbilt University as a Professor of Psychiatry and Pharmacology and Director of the Psychopharmacology Center. Herb has had such a rich career that it's hard to know where to start. Probably the best place is what's the most exciting thing you're working on now and if you could elaborate on where you think this is going to take us.
HM: The most exciting thing I'm doing now is looking at the new antipsychotic drugs in the treatment of schizophrenia and their many applications, and, having the continuing opportunity to integrate my basic science interest with the clinical. They've always been an important part of me. It's why I went into this field; because I couldn't decide between the two of them and it's one of the unique fields in medicine, where I could really do both. We're having a tremendous amount of fun, seeing how good these drugs really are, what their strengths and limitations are, where the new drugs, the olanzapines, risperidones, sertindoles and ziprasidones, fit into treatment strategies, as well as understanding the basic mechanisms and trying to push ahead to the next generation of antipsychotics, using these drugs as tools to understand what schizophrenia is all about.
SK: When do you think there will be the next generation of antipsychotics?
HM: Well, the most immediate thing you can see are some drugs that are antipsychotic without directly blocking the dopaminergic system, drugs like MDL 100907 and finanserin, which are serotonin$_{2A}$ antagonists with little or no effect directly on the dopaminergic system. What I'm really passionate about is trying to get a way to intervene in schizophrenia before the psychosis begins. We know this is more a developmental disorder and I have found, it's not a unique finding, but certainly confirming it, that the core cognitive deficit in schizophrenia, the problems in attention and executive functioning, in memory and learning are present at a fairly significant level before the psychosis emerges. These deficits, much more than the delusions and hallucinations, set a limit on how people with the illness function in the world. So what we're trying to do is identify people through syndromal characteristics. I'm sure, in the next five years, we're going to have genetic markers for this and, once we've got them, we will

* Herbert Y. Meltzer was born in Brooklyn, New York in 1937.