Central Office

Leonardo Tondo: Interviews with Pioneers

Frederick King Goodwin

On manic-depressive illness and longitudinal studies

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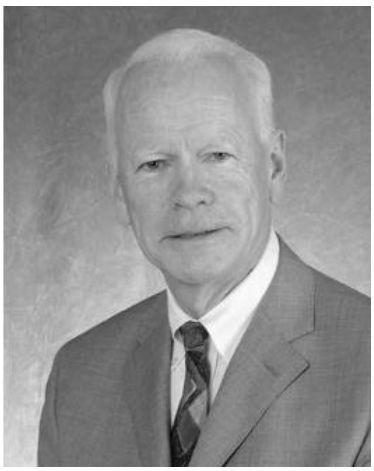

Biographical notes[1]

Frederick K. Goodwin was born in Cincinnati, Ohio, on September 21, 1936. In 1945, the family moved to the Washington D.C. area, where his father worked for decades as a senior leader in the Department of Labor. He graduated from Georgetown University in 1958 with a major in philosophy and received his medical degree in 1963 from Saint Louis University. In the same year he married Rosemary with whom had three children. He completed a residency in psychiatry at University of North Carolina, Chapel Hill. After that he returned to Washington and joined the National Institute of Mental Health (NIMH). He was well known as one of the founders of psychopharmacology, and international expert on manic-depressive illness. He co-authored the standard text in the field, *Manic-Depressive Illness*, often nicknamed as *The Bible*.[2] Its first edition was published in 1990 with Kay Redfield Jamison (1946–).[3] It became an instant classic, gave them an international reputation, and it is still considered one of the most authoritative and comprehensive references on bipolar disorder. Goodwin always underscored the importance of authoring a textbook oneself, or with a single coauthor, an old-school approach. Both editions of the book (1990 and 2007) had the same title in honor of Emil Kraepelin (1856–1926),[4] who used the term *manic-depressive illness* to describe the illness later termed *bipolar disorder*.[5] Goodwin considered Kraepelin's view more valid than *DSM*-based definitions of bipolar illness and major depressive disorder. The textbook details clinical features, pathophysiology, and treatment of the illness, covering not only pharmacological approaches but also integrating findings from neurobiology, epidemiology, and psychosocial research.

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[1] Biographical information is based on: Ghaemi S. Nassir J Clin Psychiatry 2020;81(00):20f13706

[2] [a]. Goodwin FK, Jamison KR. Manic-Depressive Illness. 1st ed. New York, NY: Oxford University Press; 1990. Kraepelin E. Manic-Depressive Insanity and Paranoia. New York, NY: Arno Press; 1976. [b]. Goodwin FK, Jamison KR. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. New York, NY: Oxford University Press; 2007.

[3] American clinical psychologist and writer mainly on bipolar disorder, an illness she has suffered from since her early adulthood. She holds the post of the Dalio Professor in Mood Disorders and Psychiatry at Johns Hopkins University School of Medicine.

[4] German psychiatrist considered the founder of modern scientific psychiatry, psychopharmacology and psychiatric genetics.

[5] Kraepelin E. Manic-Depressive Insanity and Paranoia. New York, NY: Arno Press; 1976 (last orig. ed. 1921).

During his career at US National Institute of Mental Health (NIMH), Dr. Goodwin worked with William "Biff" Bunney (1930–)[6] to advance research on mood disorders. In the 1970s, he became Chief of the Laboratory of Clinical Psychobiology, then NIMH Scientific Director and Chief of Intramural Research (1981–1988), and head of the Alcohol, Drug Abuse, and Mental Health Administration (ADMHA) until 1992, when he became director of the NIMH until 1994. During his time at NIMH, Goodwin supported researchers not for specific projects but for their research programs in order to encourage innovation and even risky ideas, with the hope that useful advances would emerge. He was an advocate for integrating biological psychiatry into clinical practice and supported research aimed at understanding genetic, neurobiological, and environmental factors involved in psychiatric disorders. He promoted large-scale, multi-center studies to better understand the efficacy of various treatments for mood disorders and to identify biomarkers associated with these conditions. He was a strong advocate for evidence-based medicine in psychiatry, emphasizing use of clinical research to guide treatment decisions. He believed in the integration of scientific research and clinical practice. His clinical research focused particularly on the recurrent nature of manic-depressive illness and the importance of mood-stabilizing medicines, such as lithium. His work helped destigmatize mood disorders and underscore the need for long-term management strategies to prevent relapses. After leaving the position of NIMH Director, Dr. Goodwin remained active in research, teaching, and writing. He was a frequent speaker at psychiatric conferences and continued to contribute to scholarly publications to the end of his life. He authored over 500 articles, book chapters, and reviews in the field of psychiatry ranging from neurobiology of mood disorders to psychopharmacological treatment strategies.

Fred Goodwin was a public person and often present in the public press. His office contained pictures of him with the pope and presidents. He ran into major troubles when the *Violence Initiative* for research was proposed to reduce violence in American inner cities in 1992 when he was the director of the ADAMHA. It was supposed to be a large-scale program of research aimed at identifying children and adolescents who may be biologically or genetically predisposed to violence. The project should have included interventions and targeted treatments diverting youth from possible future violence or time in prison. Controversy over it gained momentum when Goodwin compared youth behavior to that occurring in the jungle among primates. The reasoning behind this statement was grossly misinterpreted by the press and was immediately taken by Peter Breggin (1936–)[7] who fiercely opposed biological explanations of crime. Breggin claimed that Dr. Goodwin's research aimed at using psychiatric drugs to control the behavior of inner-city minority youth and considered this to be a racist proposal. However, supporters of the proposal considered it a legitimate and socially useful research topic which had become a victim of political correctness. Despite Goodwin's apologies, he had to resign from his position as Director of ADAMHA in 1992.

In addition to his publications, Fred Goodwin launched a highly successful radio program in 1997, *The Infinite Mind*. It was broadcast for about 10 years and was based on interviews of people about scientifically sound topics that would be accessible to large audiences. But an article in the *New York Times* on November 21, 2008, wrote that Goodwin publicized the use of drugs without

[6] William E. Bunney, is a neuroscientist who studied the genetics of major depressive disorder, schizophrenia, and bipolar disorder.
[7] American psychiatrist, fierce opponent of psychopharmacology and major supporter of psychosocial interventions (psychotherapy and empathy).

disclosing that he had received large sums of money from the drug industry nor that his radio program was funded by drug companies. The senior executive producer of the broadcast said that Goodwin had not disclosed the funding in violation of a conflict of interest disclosure in his contract. Goodwin replied that the producer knew about his educational speaking and consulting activities for pharmaceutical companies. A series of hearings followed, with the result that the program was terminated at the end of 2008. The situation sparked major discussions within the medical community about transparency, ethics, and the influence of the pharmaceutical industry in psychiatry.

Dr. Goodwin was awarded, among others, with the *Hofheimer Prize* from the American Psychiatric Association, the *International Anna-Monika Prize for Research in Depression*, the *Edward A. Strecker Award*, the *Nola Maddox Falcone Prize* from the National Association for Research on Schizophrenia and Depression (NARSAD, now known as the Brain & Behavior Research Foundation, BBRF), the *McAlpin Research Award* from the National Mental Health Association, the *Distinguished Service Award* from the National Alliance on Mental Illness (NAMI), the *Research Award from the American Foundation for Suicide Prevention*, and in his final years, the *Aretaeus Prize* from the late Athanasios Koukopoulos.

Frederick King Goodwin died on September 10, 2020, in Washington, DC, from congestive heart failure. He had suffered of Parkinson's disease which was a topic of his early research when he was studying psychotropic effects of L-DOPA.[8] He was survived by his second wife, Sheila; his children, Kathleen, Fred, Jr., and Dan; 10 grandchildren; three siblings, other family and many friends. He was preceded in death by his fraternal twin brother as well as Rosemary, his first wife of nearly 50 years.

About the interview

I arrived late for two reasons: one is that I first went to the wrong office since the buildings of the National Institutes of Health are scattered over a huge piece of land. In addition, I had not considered the traffic from Baltimore (where I was staying with friends) to Bethesda. Finally, sweating and particularly intimidated by the importance of the interviewee, I arrived at his office, a large room with many windows looking over other brick buildings typical of constructions in the 1970s. Dr. Goodwin told me that since I arrived late, he could devote only 30 minutes to my interview but in the end, the interview lasted longer.

Bethesda, March 1, 1990

LT: What do you think about the current status of research?

FKG: I think that modern research will become preoccupied with data collection and data analysis and our capacity to generate data has exploded so fast that our capacity to analyze it in a sophisticated way runs the risk of losing the special creativity of the thinking behind the data. We

[8] Bunney WE, Janowsky DS, Goodwin FK, Davis JM, Brodie HK, Murphy DL, Chase TN. Effect of L-DOPA on depression. Lancet. 1969; 26: 885–886.

may be doing more and more elegant studies of less and less interesting things. In the old days when clinical observers and clinical scientists were the same thing, you could be puzzled by a patient and have enough time to think through what that might mean and to collect observations at a slow enough pace as to allow you to keep up with the data. That's not so likely anymore, and it is one of the things I was surprised and disappointed of in the process of writing this massive book that we just finished, which is the first book which actually has been written on the subject [of manic-depressive illness] in the last 35 years [see footnote 2]. I mean, there have been edited books, but the idea of two authors sitting down and actually pulling together the literature from every field from biology to clinical description, from natural history to psychology had not been attempted since Campbell[9] did it in 1953. One reason for the delay was that the publication occurred in the face of data explosion and both my coauthor, Kay Jamison, and I were surprised at the decline of scholarship and the decline of the tradition of tracing the history of ideas. Perhaps twenty years ago when a paper was written there was more of a tendency for the author to trace the origins of the idea, to write a longer introduction and give a sense of continuity. Now, introductions to papers by and large are getting shorter, much more space is dedicated to the Methods section and particularly to data analysis. Often, you get the feeling that the concepts are being driven by the statistical analysis and not the other way around. People use multivariate techniques and let powerful computer-based driven statistical analyses sort out the dependent variables. Then there's something that we're losing sight of. So, I think it's very valuable that you are doing a book that steps back from raw data and asks people who thought about the data to reflect upon what they were thinking and why.

LT: How did you start and get interested in research in psychiatry?

FKG: Well, I was supposed to be a surgeon[10] but when I was in medical school my surgery professors included two distinguished men, Rollo Hanlon (1915–2011)[11] and Ted Cooper (1929–1993).[12] Cooper went on to become the assistant secretary of health, a top health official in our government and he's now the president of one of a large pharmaceutical company.[13] I was a good student in surgery and I liked operating and did some experimental surgery in the laboratory as well as scrubbing in with senior surgeons to help with their operations. I did so until my last year of medical school when I was working in clinics where I could never finish: patients would still be there at 9 o'clock at night and my waiting room would be full. Cooper asked me one day what the problem was and so he said "let me sit in with you and see if I can help you figure out what's wrong." At the end of an afternoon he said, "Fred, I think you should be a psychiatrist." I was, of course, crushed because I thought that it was a put-down. What he had observed was that I wasn't finishing because I was listening to the patients, responding to them and hearing about their problems in their lives, and that was taking more time than was allocated. He said: "You would be

[9] Robert Jean Campbell (1917–2020). American psychiatrist who wrote the *Psychiatric Dictionary*, originally published in 1953 (last ed. 2009). The book became a fundamental reference work in psychiatry covering essential psychiatric terms, concepts, and practices.
[10] Once again, the interesting liaison between surgery and psychiatry (see Perris' interview).
[11] Rollins "Rollo" Hanlon. American cardiac surgeon.
[12] Theodore Cooper. American heart surgeon who served as Assistant Secretary for Health helping shape policy on heart disease, nutrition and AIDS.
[13] The pharmaceutical company was Upjohn where he served as chairman and chief executive until his death in 1993.

frustrated as a surgeon because you wouldn't have time to talk to patients as human beings and suggested you would do better in psychiatry." So, I did.

Now how I got into depression research was an accident. I went to the NIMH to interview with Lyman Wynne (1923–2007) [14] and Seymour Kety (1915–2000) [15] who at that time were studying the psychosocial and biological aspects of schizophrenia which was becoming my principal interest. When I was a resident in the early '60s, the family dynamic theories of schizophrenia were very intellectually stimulating in this country. The notion of communication patterns in some way having distorted in the developing brain of the young schizophrenic was fascinating. On the other hand, the biological position as represented by Kety's studies with the genetics of schizophrenia also was fascinating. But there was a mistake in the scheduling of the interviews, so when I arrived at NIMH from North Carolina where I had been resident neither Kety nor Wynne was in town. Wynne was at that time a leading researcher in the family dynamics of schizophrenia and later was professor of psychiatry at the University of Rochester. However, that area of research just died out because they couldn't replicate the original findings of Wynne and Singer (1921–2003) [16] which appeared to be the result of brilliant clinical intuition which could not be replicated or verified. So, in any case I was becoming more interested in schizophrenia.

At that time, in my residency, depression was not a very interesting subject; drugs were just beginning to be used but there was no sense of any rationale in their use. They were being used in an entirely symptomatic way, kind of helter-skelter: try this, try that, in a totally random way. The intellectual formulations in my department in training were based on psychoanalytic-psychodynamic models regardless of the diagnosis of the patient. Every patient had to have a conflict formulated, and so forth. So, when I came up to interview at the NIMH, I encountered the absence of the two people in whom I was most interested in meeting and with whom I had corresponded. Because the secretary in the director's office didn't want me to go away empty handed, she scheduled a meeting with William Bunney who at that time was just getting started in studying biological theories of depression. He had not been trained in biological areas but had become very interested in them. As it turned out, I interviewed with him because he was the only one around who had time. He showed interest in me because I had studied biochemistry at NIH during summers as a medical student and had published some papers in biochemistry in an unrelated area. He indicated his intent to get people with publications in biochemistry who were psychiatrists into his program. Bunney was very energetic and exciting and so I went to work for him and with his associates John M. Davis (1933–),[17] Jan Fawcett (1934–2022),[18] and Dennis Murphy (1938–2017).[19] This original group of Bunney, Fawcett, Davis, Goodwin, and, Murphy, all were within two years of each other in age and training. It was the beginning of our careers.

[14] Wynne Lyman C. American psychiatrist and psychologist known for his work in family therapy and schizophrenia research. His contributions significantly advanced the understanding of family dynamics in mental health.
[15] Kety Seymour S. American neuroscientist and psychiatrist who researched in biological psychiatry, especially in understanding the genetic and biological bases of schizophrenia.
[16] Margaret Thaler Singer. American clinical psychologist known for her research on schizophrenia and family therapy.
[17] Davis John M. American psychiatrist interested in maintenance treatments with antipsychotics, mood stabilizers, and antidepressants.
[18] Fawcett Jan A. American psychiatrist, educator, known for his extensive research on depression and suicide prevention.
[19] Murphy Dennis L. (1938–2017): A prominent American psychiatrist and neuroscientist, a leading figure in neuropsychopharmacology.

Additional colleagues included Julius Axelrod (1912–2004), Seymour Kety (1915–2000), and Joseph Schildkraut (1934–2006).[20]

I had the advantage of being naïve. I think that's important in some areas of science. When I came into the depression field, I didn't know much about depression. For example, I didn't know that everyone assumed that mania and depression were opposite states, that was the gospel of that time because of the catecholamine hypothesis. When I started seeing patients for clinical studies, one of the things you asked in your letter was about the antidepressant effects of lithium, that was counter-intuitive at that time. The early papers on lithium, notably those by Schou (1918–2005),[21] Amdisen (1925–1990) [22] and Hartigan (1917–1968) [23] all said that lithium did not have significant antidepressant effects. Moreover, nobody expected it ("How could a drug which was antimanic also be antidepressant?"). The prevailing theory, at least in the US, at that time was that manic-depressive disorders must, respectively, involve excesses and deficiencies of catecholamines.[24]

LT: That was when?

FKG: 1964

LT: Some years before Schou published his paper on lithium prophylaxis.

KFG: Yes, Schou's prophylactic paper was published in 1967, but Schou published a very important paper in 1963 on the normothymic mood-normalizers; it was a theoretical paper. I wasn't aware of that paper at that time, but Schou actually suggested that we should look at drugs like lithium and imipramine as having effects on both manic and depressive states. Nobody in America was particularly familiar with Schou's 1963 paper; instead, the driving force was the catecholamine hypothesis supported by Schildkraut, Bunney, and Davis.[25]

I had early on a fascinating patient when we were looking at the relationship between lithium and the timing to response to lithium and the time to relapse when it was withdrawn. We had theoretical ideas about trying to understand the relationship between biochemical changes and clinical changes. We were trying to study the sequence of daily changes in behavior in relation to the sequence of biochemical changes that could be measured in the blood, in urine, and in evoked cerebral potentials. Our technique was to have periods on and off lithium and my job in that study was to supervise the clinical trials. The nurses were doing double-blind assessments twice daily with standard clinical ratings. I was doing intensive daily evaluations of the patients and I was also

[20] Axelrod Julius. American biochemist who won the Nobel Prize in Physiology and Medicine in 1970, shared with Bernard Katz and Ulf von Euler for the studies on catecholamines.
[21] Schou Mogens. Danish psychiatrist who demonstrated the effect of lithium in the prevention of manic-depressive recurrences.
[22] Amdisen Amdi Blichfeldt. Danish psychiatrist, known for the understanding and clinical application of lithium therapy in psychiatry establishing standardized methods for monitoring lithium treatment, thereby enhancing its safety and efficacy.
[23] Hartigan Geoffrey Philip. The use of lithium salts in affective disorders. Br J Psychiatry. 1963; 109: 810–814.
[24] [a]. Dunner DL, Cohn CK, Gershon ES, Goodwin FD. Differential catechol-O-methyltransferase activity in unipolar and bipolar affective illness. Arch Gen Psychiatry. 1971; 25: 348–353. [b]. Dunner DL, Goodwin FK, Gershon ES, Murphy DL, Bunney WE Jr. Excretion of 17-OHCS in unipolar and bipolar depressed patients. Arch Gen Psychiatry. 1972; 26: 360–363.
[25] Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965; 122: 509–522.

held blind to their treatment status. In the course of this work we published a single-case report of a patient being withdrawn from lithium. I began to notice that this patient was having many mixed states and that both the manic and depressive features seemed to respond to lithium. I went to Dr. Bunney with that observation and he was very skeptical as he should have been and he assumed that it was just my clinical inexperience that I was being influenced by subjective reports from the patient. After we finished our study, the same patient later went into a protracted depression and was again treated with lithium (to which I was blinded). In the 4th and 5th week of treatment with lithium, I observed a very substantial improvement in her depression. When lithium was discontinued, she relapsed, and this pattern was repeated twice more. I was convinced that she was receiving an antidepressant, but when we broke the blind, I found that she had been given lithium. Then Bunney became more interested. We looked back at the early literature, including reviewing primary research reports, and found that no one had evaluated effects of lithium on depression for longer than three weeks. These findings, together supported our proposal that lithium may indeed have an antidepressant effect but that it may be delayed into the 4th and 5th week. We then set up a study to test this, at first with 12 patients and then expanded to 52. Focusing on the antidepressant effect of lithium, in 1968–1969, we compared clinical characteristics between responders and nonresponders and we found that the responders were largely people we called "cyclic depressives."[26] This was prior to the unipolar-bipolar distinction among depressions having been established, led by proposals by Karl Leonhard (1904–1988) in 1968.[27]

LT: In 1967 or 1968.

FKG: Leonhard maybe had just published it but it hadn't become widely known in the American literature, and further support for a bipolar/unipolar distinction by Jules Angst (1926–) [28] and George Winokur (1925–1996) [29] came after our observations made in 1966–1967.[30] We were using the concept of cyclic and noncyclic. We were supported in emphasizing recurrence in depression by the work Tom Wehr (1944–) [31,34] as I well as your work with Athanasios Koukopoulos (1931–2013) [35,36] The concept of recurrence in major depression may be as important as polarity. Cyclicity should be looked at in its own right, independent of polarity and much of the confusion in the literature today about the prophylactic effectiveness of drugs like lithium compared to tricyclic antidepressants among unipolar patients is a confusion between cyclic unipolars and noncyclic

[26] Goodwin FK, Murphy DL, Bunney WE Jr. Lithium-carbonate treatment in depression and mania. A longitudinal double-blind study. Arch Gen Psychiatry. 1969; 21: 486–496.
[27] Leonhard K. Über monopolar und bipolar endogene Psychosen [On monopolar and bipolar endogenous psychoses]. Nervenarzt. 1968; 39: 104–106. German.
[28] Angst J, Felder W, Frey R, Stassen HH. The course of affective disorders. I. Change of diagnosis of monopolar, unipolar, and bipolar illness. Arch Psychiatr Nervenkr (1970). 1978; 226: 57–64.
[29] Winokur George. American psychiatrist who contributed to the classification and genetics of mood disorders. His seminal studies are known as the Iowa-500. The paper mentioned here is: Winokur G, Morrison J, Clancy J, Crowe R. The Iowa 500. II. A blind family history comparison of mania, depression, and schizophrenia. Arch Gen Psychiatry. 1972; 27: 462–464.
[30] The only available publication on the subject of distinction around those years, seems to be: Winokur G. Clayton P. Family history states. I. Two types of affective disorder separated according to genetic and clinical factors, in Wortis J (ed): Recent Advances in Biological Psychiatry. New York. Plenum, 1967. Related papers are: [a]. Perris C: A study of bipolar (manic depressive) and unipolar recurrent depressive psychoses. Acta Psychiatr Stand [Suppl]. 1966; 194: l–189. [b]. Winokur G. Is there a common genetic factor in bipolar and unipolar affective disorder? Compr Psychiatry. 1980 ; 21: 460–468.
[31] Wehr Thomas A. American psychiatrist involved in the study of the course of manic-depressive illness.

unipolars.[32] You know, in the studies of my old NIMH colleague, Robert F. Prien, PhD (1933–2009),[33] they don't really make the distinction between bipolar and recurrent unipolar depression nor between true prophylaxis and effective continuation treatment. Another important study was Schou's review on lithium in the mid 1970s,[34] in which the episode frequency of recurrences unipolar depression was similar to the recurrence rate in bipolar disorder, with an episode every 12 to 24 months.[35] In the recurrent depressives, lithium may superior to tricyclic antidepressants. Our early observations prior to knowing about a unipolar-bipolar distinction were already picking up on distinguishing cyclic from noncyclic depressions.

LT: Until now, you have spoken of depression, but when did you get interested in the induction of mania during treatment with antidepressants?

FKG: That came primarily from our interest in longitudinal studies in inpatient settings. We took advantage of our capacity to study a few patients very intensively over long periods of time. In this country much of the research is forced into being cross-sectional because patients' insurance would only cover one month of hospitalization. So, to be ethical, research has to be a very quick snapshot. The NIMH internal program which was one of the very few in the country that could admit people and keep them at no cost for as long as we wanted. Because we were interested in longitudinal studies, people said: "Why did you focus on manic-depressive illness?" We focused on manic-depressive illness for several reasons: one is that you could study the clinical states of depression, mania and euthymia in the same patient over time, and so have a handle on separating state-dependence from state-independence. You could look at temporal sequences of biological and behavioral correlations including particular biochemical changes which precede or follow a mood switch, for example. Dr. Bunney deserves most of the credit for originating that idea.[36] I think it was a very important period in the development of longitudinal studies in psychiatry because it forced us to recruit patients with enough mood switches in one year as to support study of the same patient several times. Indeed, we started with rapid cycling patients (with ≥4 episodes/year) as well as others with 2–3 episodes/year.

Because we were interested in the switch process, we recruited patients with high numbers of switches. Such patients almost always were being treated with tricyclic antidepressants. Also, because our research was totally government supported, we did not have any support for our research from pharmaceutical companies and there was no subtle tugging at us to look at effects of particular drugs.

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[32] It is likely that Dr. Goodwin refers to major depressive disorders with low or high frequency of episodes. In fact, high frequency of depressive episodes may indicate a similarity to bipolar disorder.

[33] Prien Robert F. American psychiatrist. The papers mentioned should be: [a]. Prien RF, Klett CJ, Caffey EM Jr. Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. Arch Gen Psychiatry. 1973 Sep;29(3):420–425. [b]. Prien RF, Klett CJ, Caffey EM Jr. Lithium prophylaxis in recurrent affective illness. Am J Psychiatry. 1974; 131: 198–203.

[34] Schou M. Lithium as a prophylactic agent in unipolar affective illness: comparison with cyclic antidepressants. Arch Gen Psychiatry. 1979; 36(8 Spec No): 849–851.

[35] The study in the previous note indicates that recurrences on lithium or placebo are similar in unipolar depressive and bipolar disorders.

[36] [a]. Bunney WE Jr, Murphy DL, Goodwin FK, Borge GF. The switch process from depression to mania: relationship to drugs which alter brain amines. Lancet. 1970; 1: 1022–1027. [b]. Bunney WE Jr, Murphy DL, Goodwin FK, Borge GF. The "switch process" in manic-depressive illness. I. A systematic study of sequential behavioral changes. Arch Gen Psychiatry. 1972; 27: 295–302.

LT: Do you think that pharmaceutical companies did not like this kind of research?

FKG: That's right and in fact I think there are colleagues whose observations have been influenced by their support from pharmaceutical companies.

LT: Do you think that this could be reason for their disagreement with many of your findings?

FKG: Well that is another issue. There were some very confusing papers, such as the 1982 Lewis and Winokur study on induction of mania.[37]

LT: Also Angst's papers of 1985 and 1987 or switching from depression to mania and from mania to depression?[38]

FKG: The Angst papers were also confusing and I think that Angst may have misinterpreted his own data.[39]

LT: I read them and I thought they were very good papers.

FKG: So did I. The degree to which drug company support may have influenced this work I don't know; all I know is that we were completely isolated.

LT: Drug-free?

FKG: Drug-free! That's right, a drug-free investigation. But I think that the observation of drug-induced cycling was really not a new observation, we had just made it more quantitative. Also, Tom Wehr deserves a lot of the credit for this. Very early, Tom and I both developed tremendous respect for the classical European literature, particularly longitudinal studies. Our intramural program was protected from the grant process, so we didn't have to apply for grants and therefore we had the luxury of pursuing longitudinal observations. I would say that most of the contributions we made, particularly those made by Robert Post (1943–),[40] Thomas A. Wehr (0000–), Biff Bunney earlier, myself, and Dennis Murphy (1936–2017), accounted for perhaps 20% of NIMH spending on research. That is, regarding affective disorders at least, our work represents more than 20% of new ideas and important observations, largely because we had the luxury of studying patients over long periods of time.

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[37] Lewis JL, Winokur G. The induction of mania. a natural history study with controls. Arch Gen Psychiatry. 1982; 39: 303–306.

[38] [a]. Angst J. Switch from depression to mania--a record study over decades between 1920 and 1982. Psychopathology. 1985; 18: 140–154. [b]. Angst J. Switch from depression to mania, or from mania to depression. J Psychopharmacol. 1987; 1: 13–19.

[39] Both papers (footnotes 36 and 37) deny the effect of antidepressants in inducing mania. Lewis and Winokur claim that the rate of recurrences is similar with and without antidepressants.

[40] Robert M. Post. American psychiatrist who has studied the treatment of refractory unipolar and bipolar illness, founded the International Stanley Foundation Bipolar Network, and is now attempting to address childhood-onset bipolar illness.

LT: Consequently you were creative and did not follow the usual research path.

FKG: Not following others and not doing the safest thing. In a grant system, you have highly competitive grants, it takes only one person to say that's a crazy idea to kill the score. If the payline has to be 1.4 to get funded and you have a committee of 12 people and 2 people in the committee say that's not good research, that kills the proposal. Such risks might have arisen with our circadian studies, the seasonal studies, the drug-induced cycling studies, and Bob Post's kindling studies.[41] These were major new theoretical developments in the affective disorders that led to an extensive further development by others.

LT: Would you consider these researches as the most important ones you have carried out?

FKG: In terms of my own personal research I would think that the major observations would be the first study of the antidepressant effects of lithium because I think it is theoretically important and I think it has been borne out. Secondly, I would say the controlled study showing that L-DOPA was not an antidepressant, in effect, put the catecholamine hypothesis to rest, at least the reserpine model which had been guiding the drug companies in their screening of antidepressants over the years. I think it was important intellectually for people to be able to move beyond that. Another paper that had much more impact than I anticipated was the study of the stages of mania[42] with Gabrielle Carlson (ca. 1942–) in 1973.[43] Actually I was reluctant to publish it initially because essentially it was a longitudinal observation showing the way in which the manic episode would start from a stage of hypomania and evolve into nonpsychotic mania to a psychotic delirious mania. It was really a quantitative re-statement of what Kraepelin had observed, though it was important to have that a new statement to emphasize the differential diagnosis between mania and schizophrenia, about which a lot of confusion remains. In the 1970s schizophrenia was being massively over-diagnosed and whenever paranoid symptoms were seen or thought disorders or Schneiderian symptoms were apparent, people assumed that the diagnosis was schizophrenia and that mania was not really a psychotic symptom.

LT: Do you think that that view depended on the fact that for years the only drugs available were neuroleptics?

FKG: Of course, it made a difference when neuroleptics were all that you had for treatment. But also because it was a cross-sectional observation and also because people didn't study the patients longitudinally.

LT: Were they acting following on Eugen Bleuler's (1857–1939)[44] idea?

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[41] [a]. Post RM, Kopanda RT. Cocaine, kindling, and psychosis. Am J Psychiatry. 1976; 133: 627–634. [b] Ballenger JC, Post RM. Kindling as a model for alcohol withdrawal syndromes. Br J Psychiatry. 1978l ;133: 1–14.

[42] Carlson GA, Goodwin FK. The stages of mania. A longitudinal analysis of the manic episode. Arch Gen Psychiatry. 1973; 28: 221–228.

[43] Carlson Gabrielle A. American psychiatrist specialized in childhood psychopathology and psychopharmacology and, in particular, in adolescent depression and bipolar disorder.

[44] Paul Eugen Bleuler. Swiss psychiatrist known for his contributions to the understanding of mental illnesses. He coined the terms including "schizophrenia", "schizoid", and "autism".

FKG: That's right, the cross-sectional idea of Bleuler. Somewhat later in my career came the development of techniques for the study of new metabolites in urine and spinal fluid which was important to show how to push back the limits of what you could do in a living patient.

Finally, we got the circadian rhythm area started that Tom Wehr picked up so well to raise interest in circadian physiology. Again, that came from longitudinal observations of just two or three patients in whom we kept seeing circadian sleep shifts as a function of whether they would correspond to their mood cycles. We therefore began to wonder what the connection was between the circadian physiology and the long-term rhythm of the illness. Daniel F. Kripke (1941–) [45] at that time was beginning to publish on sleep phenomena and supported longitudinal observations to follow the lead of Biff Bunney's work. He started with small studies, which generated larger studies and then the university-based investigators with large numbers of patients.

When we started the book on manic-depressive illness, we thought it would be a lot easier than it turned out to be. We were also disappointed that some of the reviewers in important fields had not checked their primary sources correctly and we found some rather large mistakes in review papers written by distinguished colleagues who obviously turned them over to junior colleagues who hadn't done a good job on scholarship. The reason it took longer than we thought is that we had to go back and do our own primary reviews in areas where I wasn't that familiar. I had hoped to rely on reviews by distinguished expert colleagues, but it turned out that there weren't really many very good review papers which you could rely on. We finally finished it and it will be out in March or April. I might add that another reason why we decided that manic-depressive illness was such a fascinating model for all those of us who came from a neurobiology perspective was that in case of manic-depressive you have six different actions of drugs to study. You can study the effects of drugs on increasing or decreasing depression, increase precipitating or reversing mania, or increasing or decreasing mood-cycles. So that's six different interactions to study.

LT: That's very interesting.

FKG: And theoretically, think about what it means to have a drug which has both anticyclic, antidepressant, and antimanic as opposed to one which is mania-inducing and antidepressant. That is, there is a clear distinction between the effects of tricyclic antidepressants from lithium based on the ability of one to precipitate mania and be an antidepressant, the other to be antimanic and a moderate antidepressant. I have always felt from a neurobiological point of view that these were the most interesting pharmacological tools and that manic-depressive illness gave us a much better chance to dissect these relationships. We were also fascinated by manic-depressive illness because even though it is the most highly genetic of the psychiatric disorders it also had a very rich literature on environmental precipitating factors and particularly the early precipitants. Indeed, that is what got Bob Post involved in the kindling models. Our findings indicated that the early precipitants were more important than later precipitants. So, we began to reason what models could explain why an illness with acquired psychosocial stress initially then became autonomous as time went on.

[45] Daniel F. Kripke. American psychiatrist who was a pioneer in the study of sleep monitoring, wrist actigraphy, and bright light treatment at the San Diego VA Medical Center in 1981.

LT: Is there a special priority in affective disorders at NIMH?

FKG: Only that it was a good model. Not that we were interested in affective disorders as a public health problem but rather that affective disorders by the nature of its symptoms and of course offered many handles for research. We didn't say this is the most important public health problem therefore we are going to study it; we said this is an illness which at the moment offers us the best chance to understand behavioral and biochemical correlations related to the mechanism of action of drugs. In fact, many of the techniques we developed for the study of manic-depressive illness are now being applied to schizophrenia. Schizophrenia is a much tougher problem, with much more heterogeneity and no chance to separate states from traits, and difficult to find drug-free patients. In many ways we've learned some of the rules of the game in manic-depressive illness. Remember that treatment of manic-depressive illness was the first in the psychopharmacology revolution, with lithium as the first drug in modern psychiatry.[46] Virtually all the redefinition of modern psychiatry and the bringing together of the analytical and biological approaches for the first time around drug effect, has all been related to manic-depressive illness.

LT: Also ECT?

FKG: I mean physical treatment and nonpharmacological new treatments including intensive light, sleep deprivation, and so forth. All of these things have been focused on where you have hypotheses to go with them. Most of the approached developed to study manic-depressive illness have been adapted to the study of other illnesses. The majority of psychopharmacology in the last 25 years has involved the broadening of applications of drugs which were initially discovered to have indications in manic-depressive illness. This was not a public health decision. I mean, if it were a pure public health decision we could have said let's focus on schizophrenia, but we wouldn't have had a clue what to do. Research cannot be driven only by health needs; it has to be driven by what's studyable. I often have to say that now to members of Congress because they often do not understand that. They say, "since more people are dying from this or that, let's study that and not this." We say we'll study what we have tools to study and push the knowledge on and maybe later on we'll have something with which to study schizophrenia.

LT: Thank you.

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