

Preface

A nationwide conference of experts from the neurosciences and psychiatry was convened by the National Institute of Mental Health (NIMH) in Williamsburg, Virginia in 1969 to review remarkable developments in recent depression research and the role of the new “antidepressant” drugs [1]. Aware that most of the findings on drug efficacy, and that the new hypotheses concerning the neurochemical bases of depression had been generated from studies with small samples of patients, and in some cases, relatively primitive methodology, senior advisors recommended development of a “collaborative” study. The study would assemble a much larger sample of patients and be aimed at definitively testing novel hypotheses about the psychobiology of depression and the basic neurochemical mechanisms of action of the then new tricyclic drugs. It would, e.g., examine changes in two or more biological systems simultaneously, something that had not been possible to accomplish previously. To accomplish that it would bring together several hospitals in order to recruit more rapidly, the large patient sample that would be required, and combine technology from laboratories of expert investigators in the pharmacology, neurochemistry, and psychology of depression.

Methodologic preparations to resolve the diagnostic issues for the study were initiated in the early 1970s. The study as a whole, was launched shortly after. The NIMH Collaborative Psychobiology of Depression Program (CDS) effort is described in detail in two papers [2, 3]. Although collaborative studies in psychiatry were, since the early Veterans Administration [4] and NIMH studies [5], now common in psychiatry they were designed almost exclusively, for the purpose of evaluating new drug treatments. The CDS represented the first effort by scientists and clinicians to use the collaborative structure to test theoretical hypotheses about the basic mechanisms underlying a specific mental disorder in an experimental framework.

After that multidisciplinary study on the “Psychobiology of Depression” conducted over a period of ten years, was completed, the late Jim Maas and I wrote later that, although successful in achieving most of its major aims, like most studies conducted during this period, it utilized an inadequate research model in its study of how the drugs acted on depression. We came to the conclusion that the majority of research, previously focused on this theme, had been pursued in the “wrong” way [6].

We then made recommendations for rectifying the central problems. The guidelines proposed were followed up in a second collaborative study with co-investigators Alan Frazer and Charles Bowden at the University of Texas at San Antonio. The results of this second study designed to follow-up unusual findings associated with the first project were published in 2004 [7]. We are aware now in 2013 that the field of study, formerly heavily invested in the neurochemistry of depression, has entered a new “era” in which genetics, molecular biology, and the direct study of brain functioning play the major roles. We are also aware that despite intensive study of the neurochemistry of the disorder and the effects of drugs, literally thousands of studies over the past four decades, we still have found no biological “markers” of the disorder nor are we “*completely clear at this point*”, as the Task Force of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) concluded, “*as to mechanisms underlying their efficacy in depression,*” that is, how the drugs bring about recovery from depression [8].

These gaps in our knowledge are mainly responsible for the fact that no new classes of antidepressant (AD) drugs have been introduced since the selective serotonin reuptake inhibitors (SSRIs) in 1979 and why “drug discovery” efforts by the pharmaceutical companies have virtually stalled [9]. The CINP Task force based their conclusion on results reviewed in 2007 of all relevant studies that investigated neural and behavioral mechanisms underlying the efficacy of the established classes of ADs. They reported that although we now know a great deal about how the drugs work, we are still unclear as to the neurobehavioral mechanisms responsible for the remarkable improvement in 50 % to two-thirds of depressed patients.

In this book I describe the “right” research model to apply in future studies and review the findings from the two collaborative studies that contributed toward closing the gaps in our current knowledge.

I hope, also, to encourage further work, utilizing our research model, to elaborate understanding of the disorder and the basic mechanisms of drug actions. It is especially necessary at this time to change the research approach lest we commit the same tactical errors in the new genetic era that we committed in the neurochemical era.

In this book, I describe the research approach, and the new findings that led to: (1) Identifying the major mood, cognitive, and behavioral components of the multifaceted depressed state; (2) Uncovering the dimensional structure of the disorder; (3) Further elaboration of the psychological turmoil that defines the experiential state of depression; (4) Proposing a new theory about its conflictual nature detailing the interaction of neurochemistry and behavior which comprise the state, and (5) Describing the impact of the antidepressant (AD) drugs on behavior and chemistry, that is, the drug-specific actions on behavior, and the onset and sequence of clinical actions that precede recovery.

In so doing, how to effect important changes in the research model applied in clinical trials and clinical research, generally, is described.

There is a need when seeking to develop new, more effective drugs, to modify the behavioral methodology and the specifics of research design in order to clarify the neurobehavioral characteristics of depression, and the basic mechanisms underlying the efficacy of established AD drugs.

The linkage between central nervous system chemistry on the one hand, and behavior and mood on the other, is strong. Any doubts about this can be erased when one considers the acute effects of alcohol, and the more awesome effects that almost “invisible” amounts of the lysergic diethyl amide (LSD) drug (measured in micrograms) can have on the psychological functioning of human beings [10]. The story behind the chemical treatment of depression, although not as sensational in its impact as the research on the effects of psychedelics, opened the door to further understanding of how the central nervous systems functions and the roots of a mental disorder. It represents only a beginning in the next era of psychobiology and neuroscience.

In today’s environment, in which serious questions have been raised regarding the efficacy of the antidepressants for the milder forms of depression, and the failure in the past three decades to uncover new classes of drugs, more effective and more rapidly acting than the established ones, new drug development has stalled and pharmaceutical companies have apparently withdrawn a great deal from the effort. In this book, I recommend ways to make studies in clinical psychopharmacology more efficient, more informative, and how to make the “clinical trial” to evaluate new putative “antidepressants”, markedly less expensive.

References and Notes

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9. The current situation was analyzed incisively in an article in a popular, non-scientific journal, the *Economist* (“Fixing the drug pipeline” (2004). 370, 37–38). It reviewed current problems in the science and marketing of the antidepressants and pointed out how despite thousands of studies conducted on putative new drugs for the treatment of depression, no new classes have been developed since the early 1980s.

10. The impact of LSD on this society during the 1960s and early 1970s provided a great example of the revolution in thinking about how neural systems communicate. The startling effects on mind and body included a “re-experiencing” of the sensual and perceptual world (Huxley A. (1954). *The doors of perception*. New York: Harper & Row). At one end it included, in its effects, waves of unbridled emotion, and at the other, inspired thoughts at a higher, spiritual level such as feeling empowered in one’s capacity to contribute to lasting world peace. What is sometimes overlooked about its impact on the human psyche, however, was that most all these effects, usually lasting 8 to 12 h, were the result of a single dose measured, not as is common for most prescribed drugs in milligrams, but in micrograms, that is, in 100 to 150 millionths of a gram, an infinitesimal or virtually “invisible” amount of the substance.

Depression and Drugs

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