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BIOLOGICAL PSYCHIATRY SKETCHED—PAST, PRESENT, AND FUTURE

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OVERTURE

It is a difficult task to capture the history of biological psychiatry in a brief essay. Let me frame this modest effort in a timeless humanistic perspective.

Psychiatry is the study and treatment of troubled mental lives. Its ultimate goal is to heal broken spirits. At its core, it is an attempt to better understand human thoughts and emotions and to allow this understanding to inform the healing arts. Despite our modern scientific hubris, we know rather little about how brains truly construct our minds and passions. Partly, this is because few scholars have come to terms with the need to understand the evolutionary neural dynamics that affective experiences are ultimately made of. It is all too easy to accept emotions as primitive "givens" and proceed toward a superficial understanding based on words, arbitrary definitions, and the quiddities of logic rather than biology. But the greater and more significant

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depths of this mystery have to be plumbed by an integrative neuroscience that has barely emerged.

It is surely not off the mark to claim that the single most important scientific question for biological psychiatry is the accurate decoding of the basic neural nature of affective values and related cognitive experiences. Emotions and moods guide most of our thinking processes and behavioral choices, whether well-arranged or deranged. Many psychopathologies arise from imbalances in these feeling systems that motivate us to think and act in certain ways. At a deep psychological level, that often goes unspoken, emotionally disturbed people have some insight into the weaknesses of their minds. They simply don't know how to manage their persistent psychic disequilibrium. They are certainly no more accustomed to thinking about these psychic forces in neural terms than are the counselors and psychotherapists from whom they seek assistance.

Taxonomic schemes that do not directly acknowledge the underlying emotional faculties of the human mind and brain must be deemed provisional approximations of the goals to which we should aspire. Brain sciences that do not acknowledge or attempt to explore how such processes motivate and guide thinking do no great service to psychiatric thought. Mind sciences that do not dwell on the complexity of the internal world, replete with all manner of feelings and cognitions, do not serve our understanding well. The cognitive, behavioral, and affective sciences must devote equal effort to understanding the embeddedness of mind in brain, body, environment, and culture; otherwise essential components will be overlooked. Only by blending these perspectives judiciously, without inflaming simple-minded polarities such as nurture versus nature, is psychiatric practice well served.

By the end of the 20th century neuroscience had advanced to a point where we now understand the brain rather well. Unfortunately, the discussion of equally important, but more slippery, mind matters continues to lag far behind. Credibly linking facts about the brain to mental functions is maddeningly difficult. There are few incentives in our current system for integrating the abundant peppercorns of brain data into an integrated psychobiological understanding. A prevailing positivistic hope has been that knowledge will emerge automatically from the raw facts like cream rising from freshly expelled milk. To an undesirable degree, theoretical views have been demoted to second-class citizenship. Accordingly, rich discussions of many key functional issues almost disappeared in neuroscience as it mastered how to milk our neural nature during the last third of the 20th century. Indeed, the very concept of productive hypothesizing came to be termed, scornfully, as "mere speculation," perhaps because too many students of the mind (and certainly too many science popularizers) forgot the difference between a "working hypothesis" and a "provisional conclusion." Major textbooks of biological psychiatry and neuropsychiatry no longer discuss emotions prominently. Some consider them needless frills that intervene between reliable diagnostic categories and descriptions of related brain changes. Often, there is little tolerance for such "middle-level" theorizing that seeks to meaningfully link brain functions with mind. One aim of this text is to reverse this trend.

Thus, I proceeded to this historical sketch with several common but oft-neglected preoccupations that continue to trouble modern psychiatric thought. How are the passions of the mind truly created? How do they become overwhelming? How can mere words help heal minds? What is the healing touch? Why are character traits so important in healers as well as patients? What is the proper role of placebos in the therapeutic enterprise? Are our diagnostic categories as sound as they could be? Such concerns led me to encourage all contributors to this book to consider the central role of thought and emotions in psychiatrically significant disturbances of the psyche. My own bias is that the next great frontier in biological psychiatry is the topic that has been most neglected by modern neuroscience—the deep neurobiological nature of affective experiences. Even though our understanding of such key issues remains woefully incomplete, we must continue to share the harvest of knowledge we already have, and thereby fertilize the field, once more, so that those who come after us are better prepared to contend with the perennial joys and difficulties of mental existence.

HISTORICAL OVERVIEW

Although human interest in the nature of the mind and its passions surely goes back to a time long before the beginning of recorded history, the systematic scientific search for the causes of psychological disorders did not begin in earnest until the latter part of the 19th century. Prior to that, the practice of psychiatry was characterized more by superstition and punishment, punctuated by occasional humane concerns. Although there were several sustained periods of enlightened care of the emotionally distraught, as in the ritual purification (i.e., "incubation" or rest therapy) approaches of the Grecian period, it is likely that one of the main functions of those whole-body, whole-mind efforts—which included athletics, baths, music, dance, and ritualized sexual encounters—was the alleviation of everyday stress and sexual inadequacy. The holistic cures of those healing temples, organized symbolically under the aegis of Asclepius, the god of health, thrived for well over a millennium, but surely the stigmatization and brutalization of serious mental ailments also remained abundant yet uncelebrated. While a humanistic tradition was sustained in many middle eastern countries, Europe succumbed to the flea-ridden plagues and narrow-mindedness of the Dark Ages for an extended period, in which harsh punishments and the demonizing of nonstandard human souls prevailed [for a more detailed historical coverage, see Andreasen (2001), Mora (1985) and Stone (1997)].

Most biological approaches to treating mental ailments during the past several thousand years have been based on unsubstantiated beliefs and wild logic rather than scientific substance. Beatings, bleedings, starvation, hot and cold water shock treatments, and restraints have all been time-tested therapeutic failures, at least in the long-term. However, various socially sustained and often effective placebo approaches have often flourished, including witch-doctoring, shamanism, and occasional trepanations of skulls to release evil spirits. Apparently our social brains respond quite

well to the sympathetic concerns of others, which may be the foundation of all pervasive placebo effects in psychiatry (Harrington 1999; Moerman 2002; Shapiro and Shapiro 2001). Of course, we now know that placebo effects have real effects on the brain (Mayberg et al., 2002), perhaps brain opioid mediated (Petrovic et al., 2002), and the intervening prosocial feelings may be mediated, in part, by endogenous opioids (Panksepp, 1998).

A few revolutionaries also made substantive biomedical advances. Paracelsus (1493–1541) enthusiastically promoted one of the few effective medicines available in his time (e.g., opioids), and in *Diseases Which Deprive Man of His Reason* (1567), he described many alchemical concoctions, some of which contained heavy metals such as mercury. We now know that some of these toxic agents can help purge the body of certain psychopathological vectors, one of which was recognized as *Treponema pallidum* in 1906—the agent responsible for causing syphilis and its resulting schizophreniform mental deteriorations. Unfortunately, the safety margin between the effective doses and lethal doses was not auspicious. The eventual discovery that induction of fevers could sometimes halt syphilis-induced mental deterioration was honored with Nobel recognition (Laureate Julius Wagner-Jauregg, 1927) for the "discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica" (Jasper, 1983).

With the emergence of the scientific tradition in the physical sciences, enlightened thinkers sought to approach human psychological problems with a new sensitivity. Benjamin Rush (1745–1813) in America, along with Phillipe Pinel (1745–1826) in France, and Vincenzo Chiarugi (1759–1820) in Italy, set in motion the "moral treatment" of the insane, even though some also advocated somatic treatments: Benjamin Rush promoted bloodletting, emetics, purges, special diets, and his agitation-constraining, straight-jacket "tranquilizing chair," while Benjamin Franklin promoted electrical therapy for various ailments. These revolutionaries helped establish havens for the mentally ill in small humanistic hospitals where they sought to create therapeutic environments that aimed to facilitate the reestablishment of emotional homeostasis. The movement was sustained and amplified by social activists such as Dorothea Dix (1802–1887). Sadly, by the end of the 19th century this model had devolved in America into the massive warehousing of cognitively and emotionally impaired individuals in large state-run institutions.

Meanwhile, with the growth of scientific physiology and biochemistry throughout the latter half of the 19th century, especially in German universities, neuropsychiatry became integrated into the standard biologically oriented medical curriculum. Indeed, modern psychiatry emerged from the successes of neurology, and the hybrid subdiscipline of neuropsychiatry still thrives (Yudofsky and Hales, 1997). However, a clear division of duties also developed—classical neurologists came to focus on standard brain abilities (i.e., sensations, perceptions, actions, and only more recently cognitive activities) while psychiatrists occupied themselves more with how people feel and how they impulsively react and choose to behave on the basis of their internal passions and other affectively experienced value systems.

Thus, the two sister disciplines, neurology and psychiatry, also commonly deal with different parts of the nervous system, the former with the somatic components and the other more with the visceral components. Theodore Meynert's 1884 textbook *Psychiatry: A Clinical Treatise on the Diseases of the Forebrain* was prescient in this regard. Since then, it has become increasingly clear that emotional regulation and psychiatric diseases are related more to frontal-limbic executive functions than to posterior cortico-thalamic, sensory-intellectual functions. Parenthetically, Meynert was one of Freud's esteemed teachers, and even after he abandoned brain approaches, Freud continued to acknowledge that his wide-ranging psychoanalytic theories eventually needed to be linked to neuroscience. He recognized that what might eventually grow from that potentially fertile hybridization could be spectacular. As Freud noted in *Beyond the Pleasure Principle* (1920, p. 60): "Biology is truly a land of unlimited possibilities. We may expect it to give us the most surprising information, and we cannot guess what answers it will return in a few dozen years. . . . They may be of a kind which will blow away the whole of our artificial structure of hypotheses." And by the end of the 20th century, his premonitions had come true to such a degree that his own conceptual ideas also seemed to be blown away, or so it seemed to many who had become disenchanted with the possibility of scientifically understanding the "mental apparatus." However, there are recent indications of resurgent interest in the relations between brain and depth psychological issues in the newly emerging neuropsychoanalytic movement (Solms and Turnbull, 2002), which seeks to build substantively on past and present discoveries.

THREE GIANTS OF THE FIRST HALF OF THE 20TH CENTURY

The three pioneers who set the stage for thinking throughout the modern phase of 20th-century psychiatry were Emil Kraepelin (1855–1926) in Germany, Sigmund Freud (1856–1939) in Austria, and Adolph Meyer (1866–1950) in America. The influence of Kraepelin's perspective, derived from the successes of German neurology, has been most pervasive, yielding a lasting influence on our conceptualization of what a comprehensive psychiatry should look like. Kraepelin, now widely regarded as the titular father of biological psychiatry, started his academic work at Dorpat University at the edge of the German empire of medical science (now the University of Tartu, Estonia), where he wrote the first edition of his seminal *Textbook of Psychiatry*, which went through nine editions between 1883 and 1927. That contribution propelled him to Heidelberg and ultimately to Munich as the implicit leader of German psychiatry. Recognition of his seminal diagnostic and pathophysiological thinking remained widespread from the latter half of the 19th century until World War I shattered the vigorous beginnings of biological psychiatry.

Still, Kraepelin had laid the essential foundations, and his approach continues to symbolically represent how scientific psychiatry should proceed [his influence is still especially clear in Axis I diagnostics of the *Diagnostic and Statistical Manual*

of Mental Disorders, Fourth Edition, (DSM-IV)]. He recognized that progress had to be based on systematic cross-sectional and longitudinal clinical observations, leading to diagnostic systematics. He recruited all possible varieties of objective measures including behavioral and cognitive as well as neurological and biochemical, to achieve the most comprehensive understanding possible in his day. Through his desire to reach a full appreciation of the organic underpinnings of pathological processes, Kraepelin gathered around him a remarkable group of talented neuroscientists who also became luminaries, such as Alois Alzheimer, Korbinian Brodmann, and Franz Nissl.

Concurrently, Sigmund Freud was abandoning his early emphasis with neurological approaches to the mind, including experimentation with drugs such as cocaine for the treatment of opiate addiction, and was setting in motion a dynamic depth psychology that eventually captivated American psychiatry. Unfortunately, Freud's psychodynamic approach, which revolutionized our views of how the mind operates with many unconscious "instinctual" dimensions and urges, did not foster a robust scientific movement to properly evaluate his own blossoming ideas. That, of course, would have been impossible in his day. Initial theory was built upon rather limited clinical observations, and then theoretical constructs were built upon other theoretical constructs, with no clear empirical operationalization or organic foundations. In the opinion of many, the resulting structure ultimately resembled a Tower of Babel, where one could not readily sift the good ideas from the bad. Freud's thesis that most psychiatric problems arose simply from psychological causes has now been largely abandoned in psychiatry, even though it is accepted that childhood trauma is a powerful neurobiological factor in disrupting mental homeostasis (Chapter 4; Heim and Nemeroff, 1999). Pathogenesis is now more commonly discussed in strictly organic terms, or at the very least in terms of psychological factors that are linked to neural substrates (Chapters 6, 7, and 8).

A new chapter in modern psychiatry opened when Adolf Meyer came to America from Switzerland in 1894, moving to Johns Hopkins School of Medicine in 1910, where, under his leadership, the university became the leading psychiatric training center in the world. He established a utilitarian psychobiological tradition in American psychiatry, which consisted of a multidimensional and systematic confrontation with patient's lives. He helped revolutionize the careful documenting of life histories and acknowledged the many psychological and biological themes that must go into the treatment of each emotionally troubled person. He emphasized the fact that all patients are unique and that one should consider all aspects of their lives in a careful workup of the individual's psychological status. His analysis of case studies led to the recognition that the systematic harvesting of certain types of personal information could make a real difference in the care and prognosis of patients. He aspired to recruit all relevant aspects into multimodal treatment approaches that suited individuals' abilities and aspirations. This holistic approach set the stage for the emergence of a uniquely American psychiatry.

The intersecting ideas and approaches of these giants permeated 20th-century psychiatry, but their different viewpoints also led to cross currents that remain to be resolved in a satisfactory synthesis to the present day. Partly this is due to the discovery of potent and highly effective drug therapies that swept most other approaches

from the scene. However, with the gradual recognition that these remarkable pharmacological advances are not the comprehensive, long-term panaceas they initially seemed to be, a consensus is once again emerging that complex systems such as the brain/mind require multiple avenues of study. One aim of this text is to promote that consensus and to help forge a greater recognition that a neuroscientific understanding of the fundamental nature of affect is an essential ingredient for future progress in psychotherapeutic practice and drug development. The brain does contain an evolved *mental apparatus*, and future progress will depend on how well we penetrate into the functional tangle of the nervous system (Chapter 20). We now know this will require a judicious blend of human and animal behavioral, brain, and mind sciences.

THREE GREAT PHASES OF 20TH-CENTURY AMERICAN PSYCHIATRY

Following the decline of German medical influence in 1914, the progression of 20th-century psychiatry emerged largely on the Anglo-American scene, at least until the most recent psychopharmacological era when new agents were discovered, around the world, to have more remarkable and specific effects on the psyche than anything discovered since morphine and cocaine. This history can be conveniently broken down into three phases of about three decades each, with the Kraepelinian approach to diagnostics and pathophysiology providing a sustained background theme for all. His systematics matured when effective medicines were discovered to treat most major disorders—with the advent of powerful medications for the treatment of schizophrenia, depression, mania, and anxiety in the 1950s. It remains controversial how much each phase advanced the field relative to the ones that preceded it. Nonetheless, each period was distinctive, reflecting, perhaps, an evolving progression of scientific understanding fraught with essential growing pains. Future progress will arise from a weaving of these strands into a whole cloth that does not yet exist.

ABOUT 1910–1940: THE MEYERIAN SYNTHESIS OF A HOLISTIC PSYCHOBIOLOGY

Adolf Meyer, from his base at Johns Hopkins, developed a well-organized "mental hygiene" approach to the treatment of the whole person. He recognized certain essentials of well-rounded psychiatric practice, centered on comprehensive life histories in which one could see the many factors contributing to psychiatric disorders. Each patient was seen as a unique individual who deserved to be treated in highly individualized ways. Pressure to pigeon-hole people into diagnostic categories was not as important as the humane multimodal facilitation of lives that had been derailed. This era could also be seen as the humanistic era of American psychiatry. Psychopathology was recognized as a response to serious life events: When terrible things happened to people, their resources to cope were compromised. Meyer's approach to a comprehensive mental status examination is still emulated today. Even if such extensive

information is no longer as coherently incorporated into the care and prognosis of troubled lives, it remains an important way of knowing patients as individuals.

The Meyerian approach also fostered research into basic biological processes related to self-regulation. One of the pioneers was Kurt Richter at Johns Hopkins who pursued superlative animal research on feeding behavior, sleep, and circadian cycles (Slavney and McHugh, 1998). The hope was that such research could shed light on human issues that needed to be understood in some causal detail in order to effectively modify the underlying biological substrates. The support of basic animal research in many modern psychiatry departments correctly continues to be regarded as a cornerstone for future progress. The recognition that there is abundant natural variability of such underlying homeostatic processes, has also fostered dimensional views of mental illness (now recognized in Axis II diagnostics of DSM-IV). The work of Meyer and others suggested that troubled people should not simply be placed in diagnostic categories; rather their various dimensions need to be viewed through the lens of qualitative life histories reflecting temperamental strengths and weaknesses. With the completion of the Human Genome Project, and the recognition of deep homologies in the brain systems of all mammals, the role of genes and evolution in the governance of personality and developmental disorders is increasingly recognized (Chapters 5, 14, and 21).

WORLD WAR II THROUGH THE 1970s: THE PSYCHOANALYTIC ERA

Although psychoanalytic ideas have been percolating in American psychology since Freud and Jung's visit to Clark University in 1909, the full impact of depth psychology on psychiatry had to await the massive exodus of psychoanalysts to England and America with the onslaught of World War II. As these energetic immigrants captivated American psychiatry with remarkable speed, there was a dramatic shift toward the psychodynamics of the mental apparatus, as well as the controversy that still surrounds "talking cures." The overconfidence of this revolution, especially in the often successful treatment of war-trauma-induced neuroses, allowed new approaches such as clinical psychology to become established as a distinct discipline, along with the resulting proliferation of new psychotherapeutic ideas. Although we now recognize that certain psychotherapies can modify the executive functions of the brain concentrated primarily in frontal lobe areas (Baxter et al., 1992; Schwartz et al., 1996), the precise factors that promote such changes remain ambiguous. It is increasingly realized that the personal emotional qualities of a therapist are commonly more important than the specific psychotherapeutic approaches he or she employs (Beutler et al., 1994). Despite the bleak overall results of scientifically rigorous outcome studies of psychoanalytic therapies (MacMillan) 1997, this era firmly established a respect for the internal dynamics of the human mind within psychiatric practice.

Indeed, Eric Kandel (Nobel Prize, 2000), a psychiatrist who devoted his professional life to the neuroscience of basic memory processes in sea slugs in the hope of deriving general principles that would translate to humans (Kandel 2001), noted that "psychoanalysis still represents the most coherent and intellectually satisfying view

of the mind that we have" (Kandel, 1999, p. 505). This comment probably speaks as much to the sheer creative richness of psychoanalytic thought as to the difficulty of developing a modern psychiatry that is based on adequate neuroscientific conceptions of the mind.

This middle era, with its shift of focus from studying the whole person to the nature of the drives and libidinal states of the mind, failed scientifically because it did not promote a solid research agenda. Likewise, the lack of replicable clinical results led to the decline of this untested (and some say untestable) theory of the mind and its influence on mainstream psychiatry, especially as pharmacological approaches were beginning to yield robust and replicable therapeutic effects.

This may again change as a new generation of scholars begins to blend neuroscience and depth psychological studies (Solms and Turnbull, 2002; Chapter 19) where mental and neuroscientific issues can be judiciously blended. The new armamentarium of brain manipulations and objective measurement tools presently offers the possibility of a renaissance for depth psychological approaches to the brain/mind (Panksepp, 1999). Whether a sustained era of penetrating "psychoethological" research will arise from the emerging neuropsychoanalytic synthesis remains to be seen, but if it does, it will only be because of the positivistic and pragmatic phase of neuroscientifically informed psychiatric research of the past 30 years.

Before turning to modern biological psychiatry, it is worth noting that the middle, psychoanalytic era, with its neglect of robust research agendas, allowed mere ideas, often endlessly debatable, too much influence on psychiatric thought. In a sense, this was also a "magical fantasy" era. Dramatic new somatic therapies, based on marginal research findings, flourished. Perhaps the Reichian concept of libidinal "orgone energy" and the resulting "orgone box" (to concentrate that "energy") could be taken as symbolic of this era: Willhelm Reich (1897–1957), whose own mental stability was eventually questioned, was convicted of fraudulent claims and died during his incarceration in a federal penitentiary. Others, like Bruno Bettelheim, generated needless guilt with concepts such as "refrigerator mothering," which allegedly was instrumental in causing early childhood autism. It took many years for that needless "guilt trip" to become an embarrassment to the discipline (e.g., Pollak, 1997).

This period also introduced radical manipulations such as metrazol and insulin-induced seizures for treatment of schizophrenia and depression. Occasional successes gradually led to the highly effective and standardized electroconvulsive shock treatment for depression (Chapters 8 and 17), but there were casualties along the way. This era of radical experimentation was capped by the most controversial treatment of all, psychosurgery (for critical overview, see Valenstein, 1973). With the wisdom of hindsight, it is all too easy to criticize these approaches, but perhaps they are understandable from a historical perspective. We should acknowledge that they sprang from understandable motives, given the historical times they were advanced. That was an era when many groups routinely inflicted incomprehensible harm on their fellow human beings—from the fields of Siberia, the ovens of Auschwitz, and "labs" of Dachau to the infection of impoverished Americans with syphilis—all in the name of political and cultural dogma and undisciplined curiosity. It was also a time when there were

few predictably effective treatments, with morphine still being very high on the list of short-term panaceas. The hospitals were full of desperately debilitated patients. Hence the field was grasping at straws, whether psychic or somatic, and the scalpels of the time were aimed directly for frontal lobes—the executive seats of human imagination, acquired valuations, and creativity (Valenstein, 1973).

Since such drastic interventions worked "adequately" in a sufficiently large number of people (at least for management purposes), it was recognized that something of importance was happening to the homeostatic imbalances of the deranged brain/mind. Indeed, the final restricted target of psychosurgical interventions, the ventromedial quadrant of the frontal lobes, is now recognized as a hotbed of emotion–cognition interactions (Rolls, 1999). What really happens in the brain/mind as a result of these powerful somatic interventions required the advent of modern neuroscience and a neurochemical understanding of the brain that eventually permeated psychiatry.

ULTRAPOSITIVISTIC PSYCHOPHARMACOLOGY ERA (1970–PRESENT)

Modern biological psychiatry started in 1952 when the French psychiatrists Jean Delay and Pierre Deniker first evaluated the efficacy of chlorpromazine (trade name Thorazine) in a variety of psychiatric disorders and found it to be highly effective for ameliorating schizophrenic symptoms. This breakthrough was based on the recent discovery of surgeon Henri Laborit that such drugs were effective presurgical sedatives, and also potentially effective in controlling the agitation of various psychiatric disorders including schizophrenia. The robust calming effects and specific reductions in the positive symptoms of schizophrenia (e.g., delusions, hallucinations, and inappropriate moods) were so impressive that the use of chlorpromazine swept through psychiatry. The number of schizophrenics that had to be chronically institutionalized diminished precipitously as soon as these agents came into widespread use.

With the recognition that one of the main targets of these agents were recently characterized dopamine systems of the brain (Arvid Carlsson, 2001, Nobel Prize in 2000), and the discovery of the various receptor molecules for dopamine transmitters, the specificity and potency of antipsychotics were honed by creative pharmacologists such as Paul Janssen in Belgium (discoverer of haloperidol, or Haldol, and also risperidone, or Risperdal). This led to our current array of atypical antipsychotics (Chapter 10), which can also alleviate some of the negative symptoms of schizophrenia (the anhedonic flattening of affect, the social isolation, and cognitive impairments often characterized as "formal thought disorders"). These newer drugs also have the advantage of few troublesome long-term side effects such as motor dyskinesias that consistently emerged after long-term treatment with the earlier, more potent antidopaminergic antipsychotics. Within a few years of the discovery of chlorpromazine, antidepressants were developed, on the heels of the serendipitous discovery that certain drugs for tuberculosis gave many patients extra enthusiasm and psychic energy [the monoamine oxidase (MAO) inhibitor isoniazid and iproniazid].

Other molecules (e.g., the tricyclic imipramine) were soon discovered to be effective in treating depressive disorders and eventually panic attacks (Klein and Rabkin,

1981). With advances in neurochemistry, the two types of antidepressant effects were narrowed to classes of molecules that could inhibit MAO or block reuptake of synaptically released biogenic amines, especially of norepinephrine and serotonin (Julius Axelrod, Nobel Prize in 1970 for "discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release, and inactivation"). This eventually led to increasingly specific agents, until we now have an abundance of selective serotonin reuptake inhibitors (SSRIs) that effectively stabilize a variety of Axis I as well as some Axis II disorders (Chapter 8), with few troublesome side effects (except for occasional emotional numbing and diminished pleasure responses such as anorgasmia). Still the long-term therapeutic mechanisms remain uncertain.

Various benzodiazepine antianxiety agents came into use in the 1960s, directly developed from preclinical animal studies that initially observed sedation and antiaggressive effects with chlordizepoxide (Librium). At this same time, the even earlier preclinical and clinical work on lithium by John Cade (1949) in Australia was gradually crafted into a treatment for manic-depressive disorders by Mogens Schou (1992) in Denmark.

These great passages of the psychopharmacology revolution have been retold many times, but never as comprehensively as in the excellent three-volume series entitled *The Psychopharmacologists* by David Healy (1996, 1998, 2000). The history of this fascinating era is detailed through a series of personal interviews with the main protagonists of the biological psychiatry revolution. In those first-person accounts, the reader can try to sort out the many controversies, linkages between lines of thought and battles over priority.

The clinical successes of the 1950s rapidly led to the characterization of various neurochemical systems in the brain [especially of acetylcholine, dopamine, norepinephrine, serotonin, and gamma-aminobutyric acid (GABA)] and the emergence of preclinical psychopharmacology disciplines that sought to characterize how these drugs operated (for summaries, see Charney et al., 1999; D'Haenen et al., 2002). It became routine to evaluate all new molecules in animals, often with classical behaviorist techniques that were not based on any theoretically coherent ideas about how psychobehavioral systems might be organized in the brain. Indeed, the behaviorists who became "opinion leaders" in pharmaceutical firms, had an active dislike of psychological theorizing and often of the brain itself. Inputs and outputs were deemed more important than the brain/mind matters that intervened.

Cranking out simple positivistic drug behavior relationships was deemed of sufficient predictive power to guide drug development. Eventually, when techniques for measuring receptor binding kinetics were developed, one could utilize test-tube assays to predict the efficacy of psychotropic agents (Snyder, 1980). Many researchers concluded it was unnecessary to worry much about psychological constructs in generating medications that could effectively treat mental disorders. An atheoretical study of input-output relations sufficed, and thus we still know little about how most of the psychiatric medicines in common use help create mental environments that are conducive to therapeutic change. This has been common in medicine where serendipitous practical advances often precede any substantive understanding.

Most of the successes of biological psychiatry have arisen from our ability to manipulate just a few neurochemical systems (Fig. 1.1). This is now understandable. There exist a limited number of "state-control" neurochemical systems that arise from discrete brainstem nuclei and ramify widely in the brain, affecting many mind functions in fairly predictable ways: catecholamines such as norepinephrine (NE) and dopamine (DA) facilitate information transmission and energize affective responses (both positive and negative), and serotonin systems generally diminish and narrow the lines of information transmission, thereby perhaps decreasing the acute effects of both negative and positive instinctual and cognitive urges. The GABA system operates through much more widely dispersed clusters of small interneurons (as well as a few long axoned pathways) to generally dampen the arousability of the brain. Hence facilitation of GABA can have striking effects on various types of overarousal ranging from anxiety to epilepsy. A brief synopsis of the biological psychiatry revolution would look approximately like this (adapted from Panksepp, 1998, p. 117):

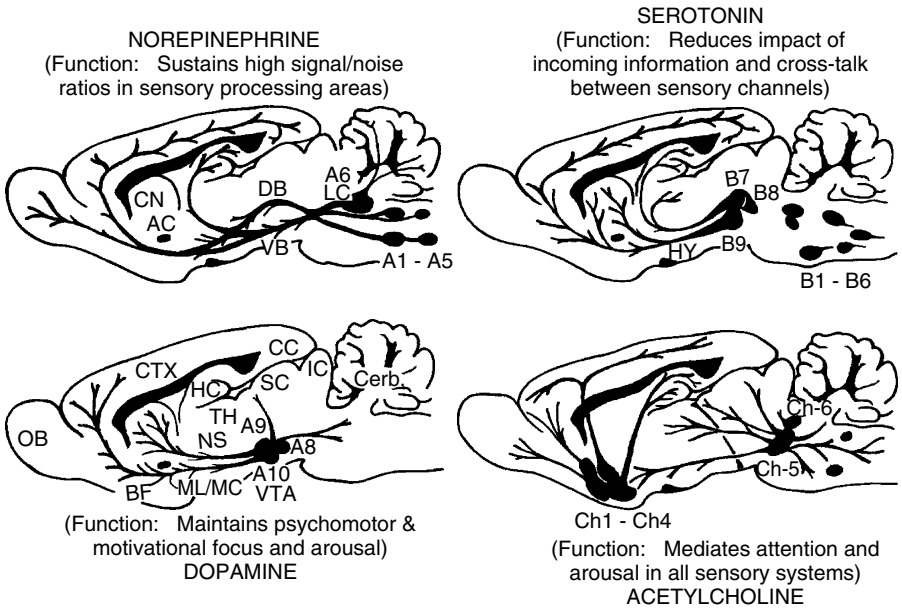

Figure 1.1. Parasagittal depiction of the dispersion of biogenic amine [dopamine (DA), norepinephrine (NE) and serotonin] and acetylcholine systems in the rat brain. LC, locus coeruleus; DB, dorsal NE bundle; VB, ventral NE bundle; CN, caudate nucleus; AC, anterior commissure; OB, olfactory bulb; CTX, cortex; BG, basal forebrain; HC, hippocampus; TH, thalamus; SC, superior colliculus; IC, inferior colliculus; NS, nigrostriatal DA pathway; ML/MC, mesolimbic and mesocortical DA pathways; HY, hypothalamus. ''A'' designations indicate major NE and DA cell groups; ''B'' designations indicate major serotonin/raphe cell groups; ''CH'' designations indicate major cholinergic cell groups. [This figure is reprinted from Panksepp (1998), *Affective Neuroscience*, with the permission of Oxford University Press.]

'Of the drugs currently used to alleviate depression, some prolong the synaptic availability of biogenic amine transmitters, while others slow degradation. In the former class are the many tricyclic antidepressants that can inhibit norepinephrine, serotonin, or dopamine reuptake at synapses. More recently, other specific reuptake inhibitors have been developed, perhaps the most famous being the SSRIs. Representatives of the other major class of drugs inhibit the enzyme monoamine oxidase (MAO) that normally helps degrade biogenic amines following release. MAO inhibitors are less commonly used than the reuptake inhibitors because they have more side effects, such as the increased toxicity of certain foods that are high in the amino acid tyramine. However, recent developments (e.g., discovery of several forms of MAO in the brain) have yielded some safer and more specific drugs of that class. Some of them, such as phenelzine, are also quite effective for other disorders, such as "social phobias," the strong discomfort that some people feel during social interactions.

The class of drugs known as antipsychotics generally dampens DA activity. Since there are several different DA receptors, modern work has sought to more specifically target the D_2 receptors, which are present in abnormally high quantities in the schizophrenic brain. Most antipsychotics are receptor blockers, which means that they prevent dopamine from having normal physiological interactions with its receptor. Other drugs that stimulate receptors are called agonists; such drugs can promote schizophrenic symptoms. For instance, the indirect agonists such as cocaine and amphetamines can induce sufficiently strong paranoid symptoms that psychiatrists have difficulty distinguishing them from the real thing.

Most modern antianxiety agents interact with their own receptor, a benzodiazepine receptor, which can facilitate GABA activity in the brain. More recently, some totally new types of antianxiety agents have been discovered, such as buspirone, which interact with serotonin receptors. With the revelation of the role of many other neuropeptides in the genesis of anxiety, perhaps specific anxieties, it is likely that even more specific antianxiety agents will be developed in the future.

Many investigators presently believe that functional psychiatric disorders result from neurochemical imbalances (i.e., lack of regulation) among many transmitter systems as opposed to a pathology in a single one, so there may be many ways to restore overall balance. The recent discovery of a large number of neuropeptide transmitter and receptor systems has opened the door to the development of a new generation of psychiatric medicines, which may modify discrete mood states and associated behavioral tendencies.'

It is also now widely recognized that the qualities of the therapist—his or her capacity for empathy—are as important for the efficacy of psychotherapy as any specific mode of treatment (Beutler et al., 1994). That is generally not thought to be the case for current biological interventions, where actions of drugs on specific chemical systems are believed to be the decisive factor in the efficacy of treatments, but many agents do work for several different diagnostic categories. For instance, SSRIs alleviate anxiety, panic attacks, and obsessive-compulsive disorders (Chapters 11, 12, 13, and 16). This may partly reflect the simple fact that broadly distributed neurochemical systems, such as the biogenic amines, are bound to influence practically all emotions and mental activities. Few emotion-specific therapies presently exist, but they may arise from the currently ongoing neuropeptide revolution (Chapter 21).

The systematic evaluation of all therapies is stymied by the existence of robust placebo effects that seem to emerge from our mysterious mental ability to improve when we simply perceive that we are being helped (Peters, 2001). In part, such effects are mediated by brain chemicals such as the endogenous opioids, which are influential in regulating pleasure and positive social feelings (Panksepp, 1998). Although some drugs and psychotherapies have effects on similar brain systems (e.g., Baxter et al., 1992), they are typically thought to access different aspects of the brain/mind. While the beneficial effects of psychotherapies are surely initiated through the higher functions of the mental apparatus (i.e., symbolically, through neocortical language functions that are uniquely human), drug therapies modulate tonic levels of arousability more directly within basic brain/mind operating systems that we share with the other animals. The convergence appears to be in the modulation of the neurodynamic tone of middle-level emotional systems of the "limbic brain."

The enormous success of the biological psychiatry revolution has led to a variety of practical socioeconomic dilemmas, related largely to the high efficacy of the available agents. They include the problems of managed care and profit-driven programs. Under such a system there are pressures to reduce type 1 errors as much as possible (i.e., the prescription of expensive therapies, when in fact they are not necessary). However, these same economic pressures tend to promote type 2 errors (i.e., claims that certain therapies are not effective, when in fact they are). Perhaps we should also be concerned about "type 3" errors (i.e., where certain high-priced drugs are aggressively pushed forward when equally effective low-priced drugs are available). When enormous economic factors come to bear on therapeutics, there is bound to be controversy about efficacy and optimal courses of action. If one can't demonstrate which treatment is unambiguously best, there is bound to be a heightened tendency by some (i.e., drug providers) to go for the more expensive options, while others (i.e., drug receivers) prefer to go for the cheaper alternatives. This makes the issue of psychiatric diagnostics and prognostics an increasingly contentious and politicized affair.

These concerns have filled the pages of important psychiatric journals for the past decade. The flagship journal in the Western Hemisphere remains the *American Journal of Psychiatry* (with its immediate predecessor, *The American Journal of Insanity*), which has now been summarizing psychiatric thought for almost a century and a half. The massive recent progress of the field can be dated by the appearance of increasingly biologized journals: first, the *Archives of General Psychiatry* in 1959 near the beginning of the psychopharmacology revolution, and then *Biological Psychiatry* in 1969, when the brain systems (e.g., biogenic amines and GABA) accounting for the initial wave of enthusiasm became well-recognized as major topics of neuroscientific inquiry. Many others have followed. We are presently at the threshold of the next great phase of the biological psychiatry revolution—with the harnessing of neuropeptidergic and molecular biological knowledge just around the corner. We can only imagine the new challenges that will need to be faced.

DILEMMA OF PSYCHIATRIC DIAGNOSTICS: DSMS AND BEYOND

Some mental disorders arise through stressful life circumstances. Others emerge more from constitutional infirmities. Nature-nurture arguments do not help us much in unraveling such intertwined complexities, unless discrete genetic differences can be discovered, as in fragile X and Williams syndrome (Chapter 14). Ultimately psychiatric thought must continue to be guided by a careful appreciation of the evolving stories of selves in action on the stage of life. Neither the "brainless" psychiatry of the middle of the 20th century, nor the "mindless" variety of the past 30 years should be taken to represent the most we can achieve. The future should yield a synthesis. However, since we have been unable to unambiguously link most mental functions to brain functions and have only been able to pinpoint biological causes for a few rare genetic disorders, we have been left no other option than to categorize mental disorders on the basis of outward symptoms. Hopefully brain imaging and new chemical measures will soon become more prominent tools in diagnostics. Meanwhile, problems of diagnostic specificity and individual sensitivity remain to be resolved (Chapter 6).

Kraepelin's original taxonomy described the outlines of major psychiatric categories still accepted today. His textbooks had clear descriptions of syndromes that we now recognize as schizophrenia, various phobias, depression, and anxiety disorders with their links to obsessions and compulsions. The modern standard classification schemes, ever since the DSM-1 of 1951, have clearly followed the Kraepelinian outline, although the early versions were well spiced with psychoanalytic perspectives on depth psychological issues.

This approach has been refined through three more cycles, with the current DSM-IV (APA, 1994) and its European counterpart, International classification of Diseases, Tenth Edition (ICD-10) (WHO, 1992), providing extensive descriptive guidance. Today's diagnostics are largely based on "what" symptoms constitute a disorder, with silence on the issues of "why" or "how" a disorder emerges from underlying psychobiological substrates. Still, the "multiaxial" approach of DSM-IV acknowledges psychological, (Axis I and II) as well as organic, psychosocial, and environmental concomitants (Axis III, IV, and V, respectively). While Axis I provides a Kraepelinian set of diagnostics of major psychiatric categories, Axis II offers a dimensional scheme for evaluating personality problems. This serves as a coherent way for clinicians to communicate pragmatically without worrying too much about unresolved etiological questions.

Although difficulties with previous versions of the DSM have been reduced, many still regard it as only a provisional scheme that needs substantial improvement (McHugh and Slavney, 1998). Several inconsistencies between DSM-IV and ICD-10 remain: for instance, in the way the two sets of guidelines handle somatoform and personality disorders, a discrepancy that contributes to international misunderstandings. The forces to construct a DSM-V are presently being marshaled, but it remains controversial whether this approach still reflects sustained progress toward a

scientifically defensible solution or simply an essential stop-gap measure that is socially needed until the etiology of psychiatric disorders are revealed. If the scheme does not carve disturbed human nature at its joints, it may actively impede scientific progress, especially where only a "natural" subset of a presumably homogeneous disorder will respond well to the therapy being evaluated.

The extent to which diagnostic schemes are influenced by societal standards is highlighted by the disappearance of homosexuality as a psychiatric disorder in the more recent versions of the manual. Partly, this has arisen from the scientific evidence that to some degree homosexuality reflects a natural variation in the organization of gender-specific brain circuitries during the second trimester of gestation (Chapter 4). It also partly reflects the emergence of new human rights movements. Scientific advances and cultural tensions will continue to permeate diagnostic practices since some "disorders" are only extremes of normal human temperamental variability (especially among the Axis II disorders), while others, to put it metaphorically, are more likely to reflect "broken parts" in the brain (most abundantly in the severe Axis I disorders). The issue of attention deficit hyperactivity disorder (ADHD) is an especially poignant example since so many children are given medications that may have potent and less than desirable long-term effects on the nervous system (Moll et al., 2001).

All simple symptom-based approaches, such as the diagnosis of ADHD, are bound to remain controversial to some extent, for there are many useful ways to conceptualize every phenomenon. It is only possible to move forward substantively on biologically based diagnostic criteria if we can objectively monitor the relevant brain systems and resulting infirmities at an organic level (Castellanos and Tannock, 2002). Such work is now advancing on various diagnostic categories (Chapters 6, 7, 11, and 14). However, continuing ambiguities create a pressure to include more and more qualifiers. The emerging problem with the complexity of DSM-IV is evident in the proliferation of subcategories of mood disorders that can defy common sense. DSM-II had only 8 types, but by DSM-IIIR there were 97, and according to Paul McHugh (2001), if you consider all the subcategories and specifiers in DSM-IV, one could categorize 2665 subtypes. This problem may continue to be endemic to appearance-based classification systems, since small differences often compel notice. The "success" of DSM-IV may partially explain the current estimate that about 28 percent of the population in America fulfill one or another of the criteria for a bona fide psychiatric diagnosis (Regier et al., 1998).

A major goal is now to seek deeper levels of understanding, which confronts us with a series of interlocking dilemmas. Epistemologically, we must resolve what major disorders objectively exist, and we must be able to specify how we know they exist, above and beyond mere surface symptoms. This question—of how we go about measuring what actually exists at an ancient neuropsychological level—has gotten a spectacular boost in the past decade from molecular biological and modern brain imaging techniques. However, so far neither brain-based criteria nor core emotional processes of the evolved aspect of the mind appear prominently in psychiatric practice (Chapter 21).

A fuller recognition of basic emotional imbalances at the core of many psychiatric disorders may also help reverse a growing problem of modern psychiatry—the marginalization of patients by making them mere consumers of pills rather than agents

in reconstructing meaningful human relationships and life insights. When the neuropeptides are finally harnessed for therapeutic purposes (Chapter 21), we may find that they work most effectively in social contexts comparable to those in which such neurochemistries first found their appointed roles in brain/mind evolution (Chapter 20). If so, some of the new medications may work optimally only when we help re-create those environments, perhaps through some type of Meyerian "sociopsychobiological" synthesis. Obviously, psychiatric disorders will continue to be permeated and modified by hosts of meta-emotional factors—above all, individual capacities for affective self-regulation and thoughtfulness.

FUNCTIONS OF DIAGNOSTICS

It is generally accepted that medical diagnosis should be directly related to scientifically demonstrated underlying pathophysiological processes. Thus all medical diagnostics, including those in psychiatry, should eventually be assisted by biological measures. This has barely started to happen in modern psychiatry (Chapters 6 and 7).

We should recall that medical diagnostics have three major functions: (1) At the lowest level, they are designed to allow clinicians some assurance that they are talking about the same problems (DSM-IV fulfills that nicely). (2) They provide an efficient way to promote consistent therapeutic approaches (e.g., a short-hand path to prescription practices). (3) Also, they provide a rapid way to think about the etiology of disorders. Perhaps the take-home message of this last function should be that we must reach a better understanding of the basic emotional systems of the brain, especially as they contribute to both psychiatric disease and health. Of course, this is based on the assumption that most psychiatric disorders ultimately reflect disturbances of affect-generating processes of the brain, a position that remains controversial among both psychiatrists and psychologists. Indeed, for the cognitive disorders of schizophrenia (Chapter 9) and some of the pervasive developmental disorders of childhood (Chapter 14), this may seem unlikely, even though changes in emotionality are surely contributory factors.

This third function of diagnostics relates directly to issues of pathophysiology and pathogenesis. With the emergence of an understanding of brain transmitter systems in the 1960s, there arose great hopes that imbalances in one or another system would map well onto psychiatric disorders. Schildkraut (1965) made the seminal suggestion that depression may arise from biogenic amine deficiencies, and norepinephrine depletion was suspected to be the major culprit. Unfortunately, the hope that different types of depression might be diagnosed by patterns of cerebrospinal amine metabolites never cashed out. However, at least one instance did bear fruit: The onset of manic episodes does correspond rather well to hyperarousal of brain norepinephrine systems (Garlow et al., 1999).

Likewise, there was optimism that certain forms of schizophrenia would ultimately reflect a variety of possible disruptions of metabolic pathways that would lead to the excessive synthesis of catechol- or indoleamine-like hallucinogens. The many fascinating hypotheses that were generated eventually led to no consensus concerning the

role of such factors. Still, these ideas are open territory for further developments. A classic psychosis can be generated by imbalancing glutamate activity in the brain with the phencyclidine hallucinogens. Thus, it is still generally agreed that schizophrenia is closely linked to imbalanced activities of certain brain dopamine systems, in concert with various other neurochemistries (Carlsson et al., 2001) and that anxiety is intimately related to the activity of GABA along FEAR systems (Chapter 16).

As far as neuroscience is concerned, there have been spectacular advances in our knowledge of the molecules that will eventually be relevant for understanding psychiatric disorders (Charney et al., 1999) but much less enthusiasm for linking such entities to mental functions. Likewise ongoing attempts to link psychiatric disorders with specific brain systems has been criticized in recent years. Valenstein (1998) provides one provocative historical overview of the many attempts and failures. He emphasized how modest real progress has been and how, "in the absence of a coherent understanding of the pathological basis of a disease, only serendipity can provide effective drugs for its treatment. Nowhere is this more evident than in an examination of the history of psychotherapeutic drugs" (quote by Sneader, 1990, in Valenstein, 1998 p. 9). But his thesis has not gone unchallenged by leaders of the biological psychiatry community (for a debate, see Valenstein and Charney, 2000). It is now generally accepted that there is much more to psychiatric disorders than neurochemical imbalances, and with recent technological advances, the neurobiological search has shifted substantially to anatomical and genetic underpinnings.

FROM PATHOPHYSIOLOGY TO PATHOGENESIS

A clear description of pathophysiological processes is essential for the generation of insights into underlying pathogenic processes. At one time, there was the hope that psychiatric disorders would turn out to be as simple as gout, where elevated uric acid levels lead to buildup at susceptible joints causing inflamed tissues and excruciating pain. Elimination of uric acid buildup (whether by blockade of synthesis with allopurinol or reduced ingestion of purine precursors) eliminates the proximal causes and all the symptoms of gout. In a sense, the classic biogenic amine theories of psychopathologies were based on the expectation that such exquisitely linear logic might apply to certain mental disorders (e.g., Schildkraut, 1965). Unfortunately, they have not. Indeed, there has been movement to conceptualize psychiatric disorder more in terms of nonlinear dynamic perturbations (Tschacher et al., 1997), perhaps with basic emotional systems being strange attractors within such hypercomplex systems.

Without adequate pathophysiological foundations, the clarification of pathogenesis is bound to be limited. The tripartite cascade of analysis applies here as with any scientific question: First, one has to identify the correlates of the phenomena in which one is interested. Second, one has to determine whether or not the correlates actually have any relevant causal influences in the system. Finally, one has to develop a "mechanistic" theory of how the system operates. This has not been achieved for any of the classic psychiatric disorders, but the goal is being approximated for certain new degenerative disorders with psychotic implications (e.g., Chapters 14 and 15).

Alzheimer's disease and other dementias are classic neuropsychiatric examples of how a careful analysis of pathophysiology has gradually led the way to a deep molecular understanding of pathogenesis. From the initial description of the pathology of restricted cortical areas, the gradual revelation of underlying genetic factors that predispose one toward such degenerative processes has finally emerged (Chapter 15). This knowledge is now slowly being translated into new and more effective therapies.

Typically, schizophrenia has been the "gold standard" by which our understanding of psychiatric disorders will be judged. During much of the 20th century there were abundant reports of both neuroanatomical and biochemical correlates, but the patterns did not begin to gel until the past few decades. The most striking discovery was the enlargement of the ventricles, which suggests a neurodevelopmental disorder that may have multiple causes (see Chapter 9). The fact that among identical twins only the afflicted siblings exhibited the brain deficit suggests the contribution of nongenetic factors. The misarrangement of nerve cells also suggests that this type of brain impairment could have both genetic and gestational (perhaps viral) underpinnings. If misconnections in the brain are the critical causal feature, as opposed to dynamic neurochemical imbalances, then even the best medicines are bound to be simply beneficial for symptomatic control of the disorder with no realistic hope for a cure, as seems to be the case in pervasive developmental disorders (Chapter 14). For instance, the selective death of GABAergic cells in frontal areas may set in motion the disregulation of dopamine systems, which can be partly alleviated by antipsychotics. However, early interventions might still offer hope for better long-term management of the disease processes.

Most psychiatric disorders exhibit substantial genetic loadings, and for some childhood syndromes, such as Williams and Rett's syndromes, the details have been worked out (Chapter 14). Studies in molecular pathogenesis continue to promise remarkable riches in understanding many neuropsychiatric problems. The pervasive consequences of trinucleotide repeats in certain genes are now widely recognized. The most prominent ones for psychiatry are Huntington's disease and fragile X syndrome, in which a good protein is converted to a dysfunctional one by the addition of "junk" deoxyribonucleic acid (DNA) to a coding site. The resulting synthesis of poorly constructed proteins has cascading consequences in brain function. The fact that certain genetic influences such as trinucleotide repeats can expand generation by generation is now seen as a potential factor for the increasing incidence and severity of certain disorders (e.g., Huntington's disease). The identification of such disease vectors permits us to offer a definite diagnosis, usually leading to the designation of a distinct syndrome. For instance, the autistic-like mental impairment of fragile X children is now recognized as a separate medical entity (Chapter 14).

With the discovery of pathophysiological correlates that characterize specific disorders, the clarification of pathogenic causes is greatly facilitated. During the 20th century, some advances were made. Perhaps the most striking was the recognition of the devastating influences of early social loss (Bowlby, 1969) and other debilitating effects of stress (Chapter 4) that have many parallels in animal models (for a review, see Panksepp, 2001). Although the discovery of this relationship in humans

came first, the cause will only be worked out by studies of other species. It is now generally recognized that the stress of social loss (whether it be in the form of separation distress or defeat in social encounters) may be a major factor in the precipitation of depressive disorders (Heim and Nemeroff, 1999). The emerging genetic data will be especially valuable in helping characterize the Axis II personality vulnerabilities that may increase susceptibility to certain emotional imbalances (Chapter 5).

The discovery of environmental vectors can rapidly lead to prophylactic maneuvers. The classic examples are the alleviation of mental retardation induced by phenylketonuria by the elimination of the toxic agent, phenylalanine, from the diet. Such a strategy, unfortunately, can currently be implemented in only a few metabolically induced disorders. For most organic disorders, the development of new therapies will require effective simulation of the disease processes in laboratory animals. To be effective, the animal models will have to be sufficiently homologous to critical aspects of a disease process so that effective translations can be made to the human condition. In the area of emotions, this remains a contentious issue that will only be resolved by the eventual achievement of practical success (Chapters 16 and 21).

Table 1.1 summarizes a highly simplified model of what a future brain-systems-based diagnostic scheme may look like. One reading of modern neuroscience (i.e., Panksepp, 1998) is that there is a limited but widely ramifying set of core emotional systems that regulate various instinctual urges critical for survival. These include systems that control appetitive-exploratory tendencies, anger-irritability, fear-anxiety, male and female eroticism, maternal nurturance, social bonding and separation distress, playful interactions, and a variety of bodily needs (thirst, hunger, and sleep). Another axis in this type of scheme would have to be based on an understanding of the status of the more general state-control systems (Fig. 1.1). Depression, for example, may reflect a global depletion of many of these neuroemotional resources (highlighted in Table 1.1 and Fig. 1.1), especially in those systems that facilitate positive emotions most prominently.

Of course, each core emotional system has complex neural substrates, with multiple interrelations among the various emotions, as well as diverse cortico-cognitive thinking structures they energize. Thus, even with such a "natural kind" of classificatory scheme, there is bound to be movement from the categorical description of major emotional disorders to the level of subspecies and mixed species. That seems inevitable as we focus on newly discovered details of the underlying processes. Still, the great challenge for the 21st century will be to coherently link the major psychiatric diseases to the basic evolved functions of the brain—to the activities of emotional systems, consciousness processes, as well as cognition and memory substrates (Chapters 2 and 3).

Such alternative conceptual schemes for the underpinnings of major psychiatric problems (Table 1.1) could also guide new drug developments and therapeutic programs in productive ways. Each emotional system is characterized by its own, at times unique, neuropeptidergic neuromodulators (Panksepp, 1998), which may become targets for novel therapeutic strategies (see Chapter 21). Viewing psychiatric disorder in this way, with reference to major emotional systems of the brain and their many general

TABLE 1.1. Postulated Relationships Between Basic Emotional Systems, Common Emotional Processes, and Major Psychiatric Disorders[a,b]

Basic Emotional System[c]	Emergent Emotions	Related Emotional Disorders
SEEKING (+ and −)	Interest	Obsessive-compulsive
	Frustration	Paranoid schizophrenia
	Craving	Addictive personalities
RAGE (− and +)	Anger	Aggression
	Irritability	Psychopathic tendencies
	Contempt	Personality disorders
	Hatred	
FEAR (−)	Simple anxiety	Generalized anxiety disorders
	Worry	Phobias
	Psychic trauma	Post traumatic stress disorder variants
PANIC (−)	Separation distress	Panic attacks
	Sadness	Pathological grief
	Guilt/shame	Depression
	Shyness	Agoraphobia
	Embarrassment	Social phobias, autism
PLAY (+)	Joy and glee	Mania
	Happy playfulness	ADHD
LUST (+ and −)	Erotic feelings	Fetishes
	Jealousy	Sexual addictions
CARE (+)	Nurturance	Dependency disorders
	Love	Autistic aloofness
	Attraction	Attachment disorders

[a]The last two columns provide hypotheses of the major relationships. Obviously, multiple emotional influences contribute to each of the emergent emotions (e.g., jealousy is also tinged by separation distress and anger), and all the emotional disorders have multiple determinants. Plus and minus signs after each indicate major types of affective valence that each system can presumably generate (adapted from Panksepp, 2000)
[b]Capitalizations are used to designate the various emotional systems to highlight the fact that these are instantiated as distinct neural entities rather than simply psychological concepts. The essential neural components constitute command influences that coordinate the basic behavioral, physiological, and psychological aspects of each emotional response.
[c]From Panksepp (1998, 2000).

modulators such as the biogenic amines, may eventually help open a route past some of the conundrums of DSM-IV (McHugh, 2001).

An understanding of the basic emotional systems we share with other mammals is already shedding important new light on acquired behavior disorders such as substance abuse. Such tendencies are based upon natural psychobehavioral urges (mediated partly

by mesolimbic dopamine systems) that motivate organisms to pursue resources needed for survival. This generalized appetitive SEEKING system of the brain energizes the instinctual apparatus for goal-directed behavior, but it can be commandeered and short-circuited "to run after its own tail," so to speak, as occurs when addictive drugs directly arouse this hedonically positive life-sustaining system. All the abused drugs from alcohol to nicotine release dopamine to some extent, leading organisms to perpetuate associated activities. As the arousal of this instinctual system becomes linked with the contingencies of drug acquisition and administration, free choice becomes constrained by the newly acquired conditional "drives." Thus this basic brain system that regulates the urge to pursue resources needed for survival becomes entrapped in a maladaptive vicious cycle. Similar processes may be operating in sexual addiction and various appetite control disorders.

This example highlights how the functional nature of certain brain systems can guide theorizing about underlying processes. However, our recognition of such systems is only the first step in the harvesting of psychiatrically useful knowledge. The actual details of how these systems operate will presumably provide insights on how they can be selectively modulated. Unfortunately, the recognition of such psychobiological constructs has been slow during this most recent molecular era of psychiatry because a widespread assumption has prevailed—one similar to that which characterized behavioristic psychology: that we could forego a deep psychological analysis of brain functions and move directly from DSM symptom-based diagnostics to underlying molecular causes. It now seems increasingly clear that this may not be possible. We do need psychological and psychoanalytic concepts to wrap our minds around what is happening to people in emotional distress. And it is not just cognitive concepts that are needed but sufficiently well-resolved affective ones as well (Ostow, 2003).

PERENNIAL PROBLEM: DISTINGUISHING AFFECTIVE AND COGNITIVE PROCESSES

Let us now briefly return to the key psychiatric issues of *affect* and *thought*: Brain imaging has finally given us an objective glimmer of the brain emotional systems in humans (Chapter 2), and the general neurogeography *is* that of the *limbic system* that Paul MacLean (1990) first brought to our attention 50 years ago. It is an everyday fact that during intense affective states, humans dwell obsessively on mood-congruent thoughts and strategies that readily flood their minds. One rotates these naturally aroused ideas persistently in the mind's eye as long as the affective states "insist," and if the ruminations (i.e., the "repetition compulsions"?) persist for too long, the resulting symptoms can become psychiatrically significant.

Although it is obvious that our thoughts can influence our feelings, for understanding psychopathology it may be more critical to fathom how our feelings channel and energize our thoughts. The prevailing assumption in cognitive science that cognitions trigger emotions, is the more obvious part of the interaction. The more psychiatrically relevant aspects may be the other way around—when perceptions enter the nervous

system, they automatically get coded for affective significance, which normally coaxes the neocortical apparatus to cogitate, but which, in its more intense forms, also sets up the potential for life-long transference relationships. In psychiatry, it may be unwise to put the more recently evolved cortico-cognitive "cart" in front of the ancient evolved "horses" that create emotional and motivational urges. Thus there is as much need for an "affective neuroscience of cognitions" as a "cognitive neuroscience of emotions" (Lane and Nadel, 2000).

The classical distinction between rational and emotional processes, however actively the two may interconnect, must be recognized in order to understand how affective states emerge within the brain/mind. Thus, investigators should begin tackling the fundamental nature of affective processes more directly than has been common in neuroscience. It presently seems unlikely that the major *sources* of our basic affective capacities—to be happy, angry, sad, and fearful—will be found in the neocortex. Although our ignorance about such matters remains enormous, we can only provoke strong emotional feelings by manipulating brain areas below the cortex, in that extensive neural territory traditionally known as the limbic system.

It remains possible that affects fundamentally reflect the neurodynamics of instinctual emotional urges in action. In advancing such a position, it is worth recalling that much of Freud's thought about the mind was based on the then "unknowable" nature of the instincts. In this regard, we should consider that affective consciousness and cognitive consciousness are quite differently organized within the brain. While their interactions provide fascinating examples of the diversity of socially derived emotional experiences—such as shame, guilt, embarrassment, and empathy—it is from our understanding of the basic, evolutionarily derived affects rather than of experientially derived cognitions that major new insights into psychiatric therapies will emerge. World events are not as critical for the elaboration of the mind's basic affective potentials as they are for its cognitive ones. Affective functions appear to be genetically disposed in the underlying action systems of the brain, almost as if our basic pleasures and pains are the "affective voices of the genes."

In considering the affect-cognition distinction, we may be wise to consider Mesulam's (2000) perspective that major brain processes can be divided into "channel" and "state" functions, with the *channel functions* corresponding to the discrete, computable forms of information processing that have traditionally been recognized as cognitive capacities. On the other hand, *state functions* correspond to the noncomputable mass-action organic processes that are broadcast more widely and diffusely throughout the brain. The basic affects are examples of such global brain states, and most should be capable of being regulated quite well, and perhaps eventually quite precisely, neurochemically. This is not to deny that cognitive readjustments may also promote desired homeostatic changes, albeit more indirectly.

Although no credible working hypothesis has been advanced on how the affects penetrate (cathect) cognitive activities, this remains one of the foremost scientific problems for psychiatry. In general, we can advance three general frameworks: (1) Affects are read-outs of higher forms of cognitive consciousness that use activities of primitive emotional systems as tokens of information in their cognitive deliberations. (2) Affects

are intrinsic aspects of the instinctual emotional systems in action. (3) Affects represent dynamic influences on quite primitive self-representational capacities that allow organisms a spontaneously active presence in the world (e.g., as developed in Panksepp, 1998). Although it is probably some complex combination of all three, I suspect we will eventually find that affects arise substantially from a very widespread paracrine broadcasting of neurochemical messages in the brain, as can be achieved by various neuropeptides (see Chapter 21).

To the extent that psychopathologies reflect such global state changes, the need for cognitive interventions may diminish and the need for organic, neuroemotional adjustments may increase. We should recognize that our neurobiological sciences are currently extremely well positioned to inform us about the nature of the general state principles that operate within the brain/mind continuum. Abundant pharmacological maneuvers already exist and will certainly improve for modulating these background *state* processes that provide a context for cognitive activities. This should be a clarion call for a new form of neuropsychoanalytic research that tries to systematically evaluate ongoing affective changes in individuals under a variety of conditions (Solms and Turnbull, 2002). Such strategies may give us a better image of the primal structure of the mental apparatus than preconceived paper-and-pencil questionnaires.

To the extent that channel functions are involved in mental disturbances, cognitive interventions will continue to be important. To readjust specific thoughts, there is no reasonable alternative but to continue to work with the details of individual lives. To understand the existential *meanings* of individual lives, we must become conversant with the patients' life stories and coping styles and identify the affectively charged associations that serve as impediments to growth. It may also be worth considering the degree to which critical aspects of individuality are lost, and any clear scientific analysis becomes problematic, when we group people into diagnostic categories that may not match brain/mind dynamics very well.

Despite the impressive advances and achievement in brain imaging (Chapters 2, 6, and 7), we should recognize and worry about how much neural complexity and individuality these pseudo-color clouds of arousal may contain. The distinct thoughts and schemes that can filter through these areas are enormous. Typically most individual-specific brain changes are discarded in generating group statistics. This brings us, again, to the managed-care issue of how important is it really for psychiatrists to understand and deal with the nuances of individual experiences? For mild depressions, the answer may be "very little," and neurochemical adjustments will tone down persistent and intrusive cognitions (Kramer, 1993). For specific phobias, obsessive-compulsive problems and perhaps panics, where cognitive behavioral and short-term psychoanalytic treatments are effective (Chapters 12 and 18), the proper answer must surely be "quite a bit."

Scientific psychiatry will need conceptualizations at various levels, ranging from "low-level" cellular and molecular models, to "middle-level" theories that focus on major functional systems of the brain, to "high-level" conceptualizations where the detailed mental events of individuals are considered. Because of the scientific successes of low-level molecular and cellular approaches, much of the field has shifted

allegiances and forged commitments only to low-level theories, and hence major texts spend abundant time on the details of neuroanatomy, neurochemistry, neurophysiology, and molecular biology and comparatively little on the human mind.

The goal of the present text is not to compete with those archival treatments of the relevant biological substrates that are now detailed in several recent compendia (Charney et al., 1999; Yudofsky and Hales, 1997; D'Haenen et al., 2002). The aim is to provide a coverage closer to the middle level of analysis (also see Bittar and Bittar, 2000), where mental faculties can be related credibly to objective brain systems in ways that may be clinically productive. Unfortunately, there has been a widespread tendency in biological psychiatry to neglect evolutionary and emotional systems in considering how the brain/mind is organized (Chapter 20), and this may now be retarding new drug development (Chapter 21).

Without a clear understanding of emotional systems (e.g., Table 1.1), we can easily lose focus if we try to leap between molecular and global diagnostic issues. Might this be one reason that advances in the discovery of new types of drugs for psychiatric illness have been so modest? We should remember that most of the psychiatrically useful drugs—the antipsychotics, antidepressants, antianxiety, anticompulsive and antimanic agents—were discovered before the advent of modern neuroscience, often through little more than trial-and-error initiatives. At best, the neuroscience of the past quarter century has largely yielded variations on previously established themes. Practically no new and effective drugs, nor insightful brain organizational concepts, have emerged from the tsunami of research that has been conducted at the molecular level. Many of us have confidence that investments in the fine-grained molecular approaches will yield strikingly new concepts (e.g., the use of neuropeptide and neurotrophin modulators as discussed in Chapter 21). At the same time, some of us suspect that the implementation of middle-level affective and emotional systems concepts will help enormously in better framing our molecular inquiries (Chapters 2 and 16).

Middle-level analyses presently provide excellent opportunities for docking mind and brain issues meaningfully and help generate new ways to look at psychopathologies and pathophysiologies and to generate new ideas for therapeutics. For instance, the existence of a generalized mesolimbic dopamine-centered SEEKING system in the brain has only been recently recognized in biological approaches to the mind (Panksepp, 1998). The system was long misconceptualized as a simple pleasure, reward, or reinforcement system because of the pervasive failure to consider *all* the behavioral and psychological evidence (Panksepp and Moskal, 2003). However, even Aristotle recognized that the appetitive function of the "soul" permeated all other parts of the mental apparatus, and it may be quite informative to conceptualize the organization of affective processes in terms of distinct, albeit highly interactive, neuromental faculties once more. As already noted, this appetitive motivational SEEKING system contributes heavily to drug addictions and the psychic excesses of schizophrenia and other psychiatric problems.

In sum, we currently know a great deal about limbic system neuroanatomies and neurochemistries, but all too little about the functional subsystems of which the "emotional-visceral brain" is composed. However, animal research, especially if we

are willing to accept the affective nature of animal life, should allow us to work out the general evolutionary principles, yielding useful concepts that should also apply to humans (Panksepp et al., 2002). Among such core neural processes, cross-species homologies do prevail. Of course, this work has no chance of clarifying the massive cognitive complexities that arise when these ancient systems interact with our expansive cortico-cognitive apparatus. To understand those interactions, a new *psychoethological* type of human mind research is needed (Panksepp, 1999). Still, a judicious blend of animal and human brain/mind research should eventually yield a new and coherent psychobiological view that is bound to be of penetrating psychiatric significance.

CODA: INTERSECTION OF 20TH-CENTURY FORCES LEADING TO A 21ST-CENTURY SYNTHESIS

There were periods during the 20th century (e.g., the Freudian era) when psychiatrists interested in the deep dynamics of the mind isolated themselves from a progressive understanding of the brain. More recently, with the neuroscience revolution and the striking molecular successes of biological psychiatry, the converse problem has emerged in some quarters—an excessive separation of psychiatric thinking from any coherent attempt to conceptualize the nature of the mind. Now that our mind inquiries can be supported by an impressive neuroscientific armamentarium, there is promise for ever more impressive docking of brain/mind issues.

Because of such advances, and only because of them, creative psychological approaches, such as those advanced by Freud, can now be tempered with neuroscience, allowing many neglected ideas to be tested rigorously for the first time. For instance, there are many neuroscientific ways to conceptualize repression, transference, projections, repetition compulsions, and various defense mechanisms. With the advent of modern brain imaging and psychopharmacology, revitalized depth psychological theories may point us toward subtle mind issues that can finally begin to be empirically resolved.

However, in cultivating diagnostic precision, we must avoid creating new disorders out of marginal differences. We must avoid constructing Kafkaesque nightmare documents similar to the *Malleus Maleficarum* that informed inquisitors of the Dark Ages, in great detail, how to identify and find witches. Without diagnostics that are linked to clear and measurable biological underpinnings, the classic tensions between the splitters and lumpers are bound to remain. There are no easy resolutions of the dilemmas such disparate views generate. With the one hand we must aspire to create a diagnostic precision that may be unattainable, and with the other we must help support the humanistic and deeply experienced affective needs of individuals in ways that are often beyond our reach. Only through a creative tension between such perspectives can a balanced synthesis emerge.

In the final accounting, we must invest in variants of the "Meyerian synthesis" by accepting the multidimensional psychobiological nature of individual therapeutic relationships. There is no substitute for the human touch. Psychological existence, of both

doctor and patient, is built upon substantive emotional interactions. The life stories of individual patients should not be forsaken, even when managed care insists that simple medications should suffice. The individuality of each person is reflected within his or her unique life encounters, diverse dispositions, and vulnerabilities. Idiosyncratic individuality must continue to be cherished. Indeed, through an increasing understanding of genetic diversity, there may be personalized psychiatric medicines in the future. We may also be better able to identify individuals who can get by on lower doses of psychoactive agent than others, thereby minimizing side effects.

To achieve this, patients should be better educated so they can become more active participants in the evaluation of their holistic treatment plans. Indeed, if new and gentle neuropeptide-based therapies do eventually emerge, we may find that they do not operate well without appropriately supportive social contexts. Such issues will be difficult to analyze empirically, but we should remain open to the likelihood that there will eventually be medicines that facilitate opportunities for people to master the emotional subtleties of their lives. In addition, optimal therapeutic effects may only emerge when patients are encouraged, as in the ancient Greek "ritual purifications," to move their bodies in emotional ways, aided by dance, music, and the other bodily passions and arts.

As we increasingly recognize the actual emotional systems that evolution has built into the mammalian brain, we will better conceptualize the psychobiological nature of mental order as well as disorders. Our emerging knowledge about the biological sources of human nature, along with our traditional human tools to listen and to empathize, may eventually help us to regulate the passions of the mind with a precision that presently seems barely imaginable. Hopefully that will be achieved in the most humanistic way possible.

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