Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter 18: The Biological Basis of Psychiatric Diagnosis and Treatment

Preamble

In the 19th century, pioneers like Thudichum believed, without clinical evidence, that disorders of the brain were linked to the chemical composition of the brain (Chapter 1). Early in the 20th century, response of specific symptoms to particular drugs (chloral hydrate, paraldehyde, bromides, barbiturates and amphetamine) reinforced that belief. In mid-century, Joel Elkes (Chapter 3) provided the missing link between physiology and chemical changes in the central nervous system shortly before the first drugs were shown to be effective for specific psychiatric disorders (Chapters 4,5 and 6).

This opened the door to attempts to link specific drugs to particular diagnostic systems described in the essay below, *Diagnostic Illusions.* In the first three decades (1949-1980) hopes of such specificity faded fast until DSM III ushered in a new multiaxial system designed to incorporate the biological, social and psychological components of each disorder. Introduced in 1980 by the American Psychiatric Association in America, it replaced the pre-existing clinical formulations with symptoms derived from a consensus of clinical experts (often after contentious debate) and largely uninfluenced by earlier knowledge from the pre-drug era concerning etiology, nosology, natural history, prognosis and outcome. Faults in the system appeared quickly and were not corrected. That the system was used primarily to justify insurance payments for drugs emphasized Axis One (Biological features) and the fact each diagnostic category included a Not Otherwise Specified (NOS) category encouraged slipshod diagnosis, a tendency that might have been checked by appropriate quality assurance criteria in clinical settings. These flaws also exposed the DSM system to corruption by industry and its hired KOL's encouraging spurious specific drug-diagnostic correlations and over prescribing (Chapters 19, 20 and 21).

The chapter on "Biological Formulations"from the book *Psychiatric Case Formulations*(Sperry et al. 1992)is part of an effort by the authors to address the problems of the DSM system by a proper use of the multi-axial format, incorporating information from earlier

classification systems. The authors collaborated in sharing their areas of expertise: Sperry (Cognitive-Behavioral), Gudeman (Psychoanalytic), Blackwell (Biological) and Faulkner (Community psychiatry). Published a quarter century ago, the text remainsremarkably relevant, testimony to the slow pace of innovation in the last four decades (1980-2019).

A biological formulation incorporates four elements:evidence for a structural or biochemical etiology; the relationship between psychiatric and physical features; the availability of biological markers, laboratory tests and imaging techniques; and treatment choice, efficacy and side effects.

Also described are features of history taken from the patient and significant others; examination of the mental and physical state; results of appropriate laboratory or test procedures;and, finally, treatment choices and prognosis. All this information is presented as both a Case Formulation and a DSM 5 axis diagnosis.

Biological Formulations

Formulation is a succinct statement of the patient's problem. It captures the essence of each person's predicament and offers an opportunity to transcend the descriptive parsimony of DSM-III-R (APA 1987) by portraying a complete biopsychosocial perspective without adding axes to an overloaded schema.

Formulation may also be performed within the framework of a particular ideology or body of knowledge, be it biological, behavioral or psychodynamic. This may seem antithetical to convergent biopsychosocial thinking but is a necessary task that illustrates a pedagogical paradox. Teaching is facilitated by considering the parts to a whole, even though such reductionism seems inconsistent with an integrated approach intended to stress systemic, nonlinear interactions.

Throughout the history of medicine, biological schemata have been part of almost every framework to understand and treat mental illness, although their significance has waxed and waned with philosophical and scientific change (Hunter and Macalpine 1964). The turn of this century marked a clear point of divergence between the proponents of descriptive and biological psychiatry and psychological theories of behavior. The former was epitomized by Thudichum,

Kraepelin and Griesinger, each of whom believed that psychiatric disorders were predominantly brain diseases. The psychological theories were represented by scientists of equal stature, including Freud, Adler and Jung. Freud, however, also relied consistently on medical models and metaphors. His preference for psychological understanding was related as much to the limitations of contemporary technology as it was to ideological principles (Jones 1953):

> "We have no inclination at all to keep the domain of the psychological floating, as it were, in the air, without any organic foundation. But I have no knowledge, neither theoretically or therapeutically, beyond that conviction so I have to conduct myself as if I had only the psychological before me."

Psychiatric Case Formulations

Interestingly enough, the biological-descriptive approach held sway in Europe, while the psychological-dynamic theories became increasingly influential in the United States. For a brief period, Adolf Meyer's psychobiological approach offered a tentative synthesis, reflected in the nomenclature of DSM-I (APA 1952). By midcentury and DSM-II (APA 1968), the pendulum had swung back in a more purely psychodynamic direction (Spitzer et al. 1980). Even while this was occurring, observations and discoveries were being made in neuropsychiatry that laid the groundwork for a paradigm shift in a more biological direction. These included the protean psychiatric manifestations of neurosyphilis, which were benefited first by fever therapy and finally by penicillin (Sirota et al. 1989). The psychiatric sequelae of viral encephalitis following the worldwide influenza pandemic also provided striking testimony for a brain-behavior link (Lishman 1978). Impairment of intellectual development and behavioral abnormalities in phenylketonuria demonstrated that such changes could be due to biochemical and not just structural lesions (Szymanski and Crocker 1989). These etiologic clues were coupled with therapeutic strategies, which, while poorly understood, produced benefits that could be explained predominantly in biological rather than psychological terms. Included were the effects of electroconvulsive therapy(ECT), insulin coma, lobotomy, the amphetamines and the barbiturates (Kalinowsky 1984).

By mid-20thcentury, the basis for a more biological understanding certainly existed, but the dominant paradigm in the United States remained psychological. Biological etiology was still

poorly understood and the treatments were either drastic, selective or relatively ineffective. As Thomas Kuhn (1970) pointed out, such an ideological plateau is customary when evidence is not yet conclusive enough to overwhelm resistance to a new paradigm, which comes from practitioners of the prevailing "normal science." In the last half of this century, four concurrent trends have pushed the pendulum strongly in a more biological direction. First came the serendipitous discovery of almost all the major categories of psychotropic drugs within a single decade (1950-1960) (Ayd and Blackwell 1984). Second, the shortcomings of American nosology revealed by the United States and United Kingdom cross-cultural diagnostic project provided an impetus toward the more rigorous descriptive and non-etiologic DSM-III (APA 1980) method of classification (Cooper et al. 1972). Third, rapid technological advances in several areas facilitated brain-behavior understanding. These included recombinant DNA methods with gene mapping (Gershon et al. 1987), receptor assays producing more specific drugs (Snyder 1985), biological and endocrine markers leading toward improved diagnosis (Whalley et al. 1989) and scanning techniques that display both structural (magnetic resonance imaging [MRI]) and functional (positron-emission tomography) aspects of brain function (Andreasen 1989). Fourth, and most recently, has been the social and economic impetus for short term, more definitive and cost-effective forms of treatment that has favored biological over psychodynamic interventions (Parker and Knoll 1990). Societal adaptation to these trends is epitomized by legislative mandates that certain psychiatric conditions (such as bipolar disorder) be considered medical diseases and afforded the same insurance benefits as other physical illness.

Whether or not the current state of knowledge amounts to a full paradigm shift remains debatable, at least in the United States. Contemporary texts devoted to neuroendocrinology (Donovan 1988) and psychopharmacology (Meltzer 1987) are certainly encyclopedic, but, as noted recently by a reviewer in the American Journal of Psychiatry (Waziri 1990), books with a descriptive or biological bent are still outnumbered by those with a psychodynamic or psychotherapeutic bias. Despite the increasing pace of biological discoveries, there remains vehement opposition and criticism of the “disease model” in psychiatric practice (Johnstone 1989).

Whatever the contemporary Zeitgeist and however dominant the biological paradigm may appear the practical question is the degree to which a core of scientific knowledge is

available and useful to psychiatrists in everyday understanding and treatment of patients. Is there a body of biological information that illuminates formulation? As Lazare (1989) noted, a biological formulation can be made based on the extent to which the information gathered meets four underlying hypotheses or assumptions:

1. The patient's problem can be understood, in part, as resulting from a known organic/medical disease.
2. The patient's problem can be understood, in part, as being related to a concomitant physical condition.
3. The patient's problem can be understood, in part, as a functional psychiatric disorder characterized by genetic transmission or biological makers that may predict treatment response.
4. The patient's condition is known to be treatable, in part, by psychopharmacologic agents or other biological treatment.

It will be noted that three of these assumptions are basically explanatory and two include treatment implications. Although the discussion that follows provides some evidence to support these hypotheses, it would be presumptive to claim proof. The brain is a sensitive and finely tuned but well-protected organ and most of our etiologic theories remain just that. In the single diagnosis where DSM-III claims an organic etiology (primary degenerative dementia), our clinical criteria are still often inconclusive with regard to underlying pathology. In one study, a third of patients diagnosed with Alzheimer's disease failed to show the appropriate postmortem neuropathologic findings to support the diagnosis (Risse et al. 1990).

Efforts to demonstrate a structural or biochemical basis for the major psychiatric disorders have been arduous and exciting but remain frustratingly inconclusive (hypothesis 1). In schizophrenia, for example, recent attempts to demonstrate brain abnormalities have focused more on neuroanatomy and neurophysiology than on biochemistry (Mesulam 1990). Neuroimaging techniques have sometimes shown an increase in the size of the frontal and temporal horns of the cerebral ventricles and a decrease in the size of the hippocampus. The ingenious application of these strategies to study the brains of monozygotic twins discordant for schizophrenia has shown that some of these structural changes are probably acquired and not genetic (Suddath et al. 1990). In addition, the overlap between "normal" controls and

schizophrenic patients is substantial; the findings are not specific to schizophrenia but can also occur in Alzheimer's disease and manic-depressive disorder. Similar uncertainties exist in interpreting the findings based on regional metabolic brain activity. Studies have reported both hypometabolism of the frontal lobe and hypermetabolism of the left temporal lobe. The findings bear an exciting correlation to the clinical manifestations of schizophrenia, with the negative symptoms of the illness resembling the results of frontal lobe damage and the positive features likened to manifestations of temporal lobe epilepsy. Again, however, it is unclear whether such changes truly reflect the underlying etiology of the disorder or if they are secondary manifestations of ongoing behavior or treatment. A recent editorial on this topic (Mesulam 1990) drew the following conclusion:

> "It is currently impossible to distinguish primary pathophysiologic processes from secondary epiphenomena or idiosyncratic observations from those that are universal. Chances are that schizophrenia is a disease of the brain but it is unlikely that such a complex, multifaceted, and fluctuating condition could be caused by fixed damage to a single brain site or neurotransmitter pathway."

Despite this absence of conclusive evidence of a general nature, the author of the editorial makes a telling point with regard to the biological formulation of individual cases in our current state of knowledge and its relationship to the use of contemporary diagnostic schemata:

The evidence strongly suggests that at least some patients with schizophrenia have detectable structural and physiological abnormalities of the brain. Item E of the criteria for schizophrenia listed in DSM-III-R, the inability to establish an organic factor, may need to be eliminated. Perhaps this will start a trend towards the total elimination of the term "organic" which is often a source of obfuscation and an obstacle to lucid differential diagnosis.

The relationship of psychiatric manifestations to concomitant physical conditions (hypothesis 2) is well accepted and has been repeatedly demonstrated. One review lists more than 50 physical disorders in different categories that may present with psychiatric symptoms (Kirch 1989). These include neurological, endocrine, metabolic, toxic, nutritional, infectious, autoimmune and neoplastic disorders. Almost half of our patients have undetected medical problems and in about half of those there is a direct contributory link to the patient's psychiatric

symptomatology or mental status (Hall 1980). The extensive literature on this topic is consistent and compelling enough to justify the conclusion reached by Jefferson and Marshall (1981) that there are few, if any, psychiatric symptoms that cannot be caused or aggravated by physical illness. The non-specificity of altered mood, behavior or perception requires a clinician to continually contend with the possibility that there maybe an underlying non-psychiatric disease process accounting entirely for or contributing to an apparent "functional" disorder.

In addition to direct biological evidence of causation, clinicians and researchers have been eager to discover diagnostic tests or markers of disease that would assist in classification or treatment choice (hypothesis 3). Such attempts have a long but frustrating history influenced as much by fashion and the theories of the time as by sound scientific evidence. Historical examples include mapping bumps on the head (phrenology), culturing the bacteria in patients' stools (intestinal autointoxication) and, more recently, measurement of urinary metabolites (the biochemical classification of depression) (Kirch 1989). Among the most consistent attempts to identify a biological basis for clinical conditions has been evidence of genetic transmission. Pedigree analysis and twin and adoption studies have provided sound evidence for the biological contribution to many psychiatric disorders. The application of this information to the formulation of an individual case, however, has relatively weak predictive power. The development of gene mapping technology (Gershon et al. 1987) may alter this by providing the means of identifying the individual's personal genotype, as is already the case for Down's syndrome. In Huntington's chorea, linkage analysis of the potential patient and of affected and unaffected relatives allows almost certain prediction of the likelihood for developing the condition (Brandt et al. 1989). Unfortunately, this is a disease with no treatment and genetic screening is fraught with psychosocial problems. Findings in major psychiatric disorders have been tantalizing but remain inconclusive. Individual kindreds have shown linkage for chromosome 11in bipolar disorder and chromosome 5 in schizophrenia, but others have not. The impediments to accurate conclusions from linkage studies are considerable and real progress is unlikely until the genes themselves are isolated (Merikangas et al. 1989). Even then it is almost certain that in psychiatric disorders more than one gene will be implicated and more than one neurochemical or physiologic process is involved.

The list of putative biological markers and laboratory tests used in psychiatric practice is extensive and includes imaging, electrophysiology, endocrinology, biochemistry, toxicology, hematology, serology and microbiology. Only a minority of those tests studied for research purposes have proven practical and useful in clinical practice, although others have certainly supported the significance of biological contributions to causation. Examples include polysomnography studies of rapid eye movement sleep (Roffwarg and Erman 1985); the use of blood platelets to study drug binding and receptor sites (Kafka and Paul 1986); and the various endocrine techniques used to study the hypothalamic-pituitary axis, including dexamethasone suppression and the thyrotropin-releasing hormone test (Loosen and Prange 1982).

It is frustrating, however, to note the disappointing outcome of some earlier attempts at investigations intended to enhance biological formulation. For a brief while, there was excitement about the ability to categorize depression into biochemical subtypes that would influence choice of medication, but it is now clear that most patients respond equally well to drugs that alter norepinephrine or serotonin or that may share some as yet unknown common mechanism of action (Kirch 1989). Equally disappointing has been the failure of the dexamethasone suppression test to achieve widespread utility. Its sensitivity and predictive value fell to unacceptable levels when the test was used in less-selected populations than those for which it was developed (Carroll 1985). It remains possible that such tests may be refined or may have a selected use in a particular context—the prediction of suicide risk is one such possibility. Another is the finding that a positive dexamethasone suppression test is correlated with a poor response to a placebo, indicating the need for pharmacologic treatment. However, response is not coupled with benefit to any particular type of antidepressant (Peselow et al. 1989)

It is in the domain of treatment (hypothesis 4) that we have attained more conclusive data. The scientific rigor of the double-blind, controlled trial at least allows some certainty in statements about the specificity of treatment outcome compared with placebo response or spontaneous remission. For both methodological and ethical reasons, such control measures are seldom applicable to outcome studies of psychosocial interventions and although alternative strategies exist, the results are often less conclusive or compelling (Strayhorn 1987).

What such studies have shown is that biological treatments make a consistent contribution to improved outcome in most of the major psychiatric disorders (Ayd 1984). The

treatment of schizophrenia has been transformed by neuroleptics, contributing to widespread closure of psychiatric facilities. A majority of patients with bipolar disorder benefit significantly and for sustained periods with the use of electroconvulsive theory, lithium and a variety of antidepressants. New categories of compounds with more specific pharmacological effects are beginning to appear. The anxiety disorders show more varied and less global benefits, although there is increasing evidence that patients with obsessive-compulsive disorder improve specifically with somatic therapy. In conditions with a clear-cut organic etiology, such as Alzheimer's disease or Huntington's chorea, patients presently remain unhelped, but our rapidly advancing knowledge of their pathophysiology will eventually yield specific biological remedies.

The quality if evidence garnered from clinical trials may be constrained by flaws or limitations in the methodology (Newcombe 1988) and however compelling the results, they sometimes fail to influence practice because of stigma and social prejudice. For example, although research evidence shows clearly that ECTis effective, opposition to its use persists, perhaps contributed to because its mechanism remains unclear, although hypotheses abound (Fink 1990). A similar controversy surrounds the use of cingulotomy for refractory obsessive-compulsive disorder (Bouckoms 1990). In the field of antidepressant drug therapy, Paykel (1989) reviewed the relevance of the research literature to clinical practice and concluded that the former certainly illuminates the latter with regard to general effectiveness but only "to some extent" in relation to specific treatment choices for an individual patient.

As in the rest of medicine, knowledge about the patient is derived from two primary sources: the history and the examination or investigation of the patient. These provide us with the symptoms, signs and markers of disease. These two sources of information will be examined to illustrate the part they play in revealing biological factors that influence each of the components of a formulation: explanation (or etiology), description (or diagnosis), treatment choice and prognosis.

Explanation and Description

Information may come from both the patient and other informants, including relatives or care providers. The latter may be most valuable in patients whose memory, judgement or insight

is eroded by biological impairment of brain function. The topics of particular relevance tobiological formulation are family history and the possible precipitants, natural history and symptoms of the condition.

In obtaining a family history, much may be forgotten and repressed or its significance missed or denied. Elicitation of a family tree across at least three generations (grandparents to children), specific questions about particular conditions and use of cultural metaphors (e.g., "nervous breakdown") may help (Baker et al. 1987). Comorbidity should be considered (e.g., alcoholism in affective disorder) and atypical features (which often breed true) noted. Polygenic inheritance, incomplete penetrance and cultural plasticity ensure that family histories of mental illness are seldom clear-cut or dramatic except in special circumstances with rare dominant pedigrees, such as Huntington's chorea or sequestered subcultures like the Amish.

History taking may reveal a number of etiologic factors that indicate a biological component. Existing medical diseases and their treatments contain manifold causes for a change in mental status, especially in anxiety and affective disorders or delirium and more rarely in psychotic phenomena;communication with the patient's primary care practitioner may prove invaluable. Cause and effect are often attenuated; a drug or disease may enhance the vulnerability to a psychiatric condition rather than being a single or simple cause for it. A 58-year-old, black, middle-aged bus driver whose hypertension had been controlled with reserpine for 10 years became severely depressed for the first time after his wife's death. His depression did not respond to grief therapy or antidepressants until after his antihypertensive medication was changed. Presumably reserpine, with its tendency to deplete catecholamines, had created a biochemical vulnerability. Until this was corrected, other usually effective treatments did not produce a response.

Information on use of street drugs or dietary substances (e.g., caffeine in coffee or cola drinks) that may mimic, provoke or exacerbate a psychiatric condition, particularly an anxiety disorder, should be requested.

Multiple organic factors may contribute to a final psychiatric outcome. For example, an 82-year-old woman living alone developed early dementia and, as a result, forgot to nourish

herself properly, then became dehydrated and finally developed pneumonia, followed by delirium.

In relatively rare instances, an occult and previously undetected organic condition will manifest itself as a psychiatric disorder. Examples are legion and include thyroid disease, pancreatic carcinoma and thiamine deficiency. At times the psychiatric presentation will be so textbook or classic that underlying organic etiology is discovered only during routine physical examination. Sometimes, however, there is a telltale amplification of particular features. The patient with myxedema underlying a depression may have extreme slowing of cognition or lethargy. The man with depression and pancreatic carcinoma may have weight loss disproportionate to change in appetite; the palpitations of a woman with thyrotoxicosis may be unrelated to psychological triggers.

An often-neglected aspect to identification of biological features of a disorder is that illnesses with a significant biochemical component tend to follow a predictable course. They behave like other medical conditions with a more or less clear-cut onset and natural history. There is an obvious point at which the person's behavior differs from his or her customary self in ways that may at first be more noticeable to others. This distinction between what is new (Axis I) and what is enduring (Axis II) is important, but not always easy to make since personality features may also modify or amplify the manifestations of the primary disorder. A successful young attorney who had always been the soul of discretion began to make sexually provocative remarks at the office and spent his entire savings on a trip to Hawaii accompanied by his secretary. Knowledge that he had a sexually repressed childhood and an unsatisfactory marriage should not postpone treatment with lithium before he bankrupts himself, ruins his career or further damages his marriage.

The fact that failure to distinguish between a new major disorder and its effects in amplifying preexistent personality traits can have a potentially disastrous impact is illustrated by the Osheroff v. Chestnut Lodge controversy (Klerman 1990). A physician was treated for seven months as an inpatient with intensive individual psychotherapy. His condition deteriorated markedly but he recovered within a few weeks after transfer to another hospital and treatment with psychotropic medication. The expert testimony that followed during legal proceedings focused on the issue of whether or not certain behaviors reflected a narcissistic character disorder

or were attributable to untreated major depression. There seems little doubt that medication was inappropriately withheld and the case has been widely construed as illustrating a paradigm clash between psychodynamic and biological models. However, it can also be seen as an issue of opinion versus evidence, with a rigid adherence to only a single approach when both medication and psychotherapy would have been indicated either concurrently or sequentially (Stone1990).

Symptoms play a vital role in indicating a biological etiology. Alterations in orientation and memory are the cardinal features of an organic condition affecting the brain. A 45-year-old woman with the history that she had been drinking excessively for serval months was brought to the emergency room by her husband while on vacation. On the morning of admission, he had found her in the hotel room confused and complaining of a severe headache. The emergency room physician diagnosed alcohol withdrawal, but the psychiatrist determined that recent alcohol consumption had been modest, the onset of headache was sudden and the confusion was disproportionate to other signs of alcohol withdrawal. A computed tomography (CT) scan revealed evidence of a recent intracranial bleed. In the absence of trauma, a diagnosis or cerebral aneurysm was made and confirmed at subsequent craniotomy.

Other Axis I conditions not categorized as organic disorders may also have core symptoms that are empirically associated with a response to drugs and linked to a hypothesized biochemical defect. In major depression, the features of a presumed hypothalamic-pituitary dysregulation manifested by “melancholic” symptoms include anhedonia, sleep disturbance, loss of libido, anorexia and weight loss. Among the anxiety disorders are the protean symptoms of autonomic arousal that have been treated for centuries as somatic in origin. In schizophrenia, the core feature is a breakdown of integration between thinking, feeling and behavior (“intrapsychic ataxia”), which manifests itself in Schneider’s first-rank symptoms that are frequently responsive to those drugs that block dopamine receptors.

Interpretation of somatic complaints is particularly vital to accurate biological formulation. Their presence may serve to obscure, amplify or mimic a psychiatric disorder. In consultation to medically sick individuals, the complaints due to organic disease may be indistinguishable from the somatic manifestations of depression or anxiety. Only such cognitive features, such as negativistic ruminations, hopelessness, suicidal ideation or unrealistic fears, may indicate the accompanying psychiatric disorder. A previously independent, active 40-year-

old business executive developed an unexplained cardiomyopathy that required intensive medical management. During a prolonged stay in intensive care, he experienced multiple complications, including deep vein thrombosis, pulmonary embolism and renal insufficiency. Assessment of a possible depression was complicated by extreme daytime lassitude, nighttime insomnia due to pulmonary embolism and fears that there was no end in sight to his suffering. His cognitive state was judged appropriate to his predicament and improved dramatically when an individual team member was assigned to explain interventions, plan daily assignments and plot a rehabilitative course to create "light at the end of the tunnel." This case also illustrates the difficulty of differentiating a major depression (obscured by symptoms of organic disease) from an adjustment disorder with depressed mood in a medical setting, where symptoms of demoralization may be secondary to a protracted stay and multiple surgical or medical interventions (Snyder et al. 1990).

The meaning of symptoms can be modified not only by the patient's bodily condition but also by the mind-set of the observer. We can all be blinded by our role as psychotherapists and by the seductive influence of psychodynamics. At times we need to be reminded that as psychiatrists we are first physicians and as physicians it is our duty to "*physich*." This imperative to seek out, identify and treat the biological components of illness is part of our social mandate. Even those of us who believe firmly in this obligation may be reminded of it by our own oversights. A few years ago, I was treating a young woman referred to me by an expert psychopharmacologist who had completed a thorough medical workup. Her atypical depression and somatic complaints yielded temporarily to medication, but since she also had severe developmental psychopathology that disrupted her work and marriage, we met weekly for psychotherapy. Engrossed in the dynamics, complacent with my colleague's work up and seduced by the early response to medication, both my patient and I minimized and misinterpreted her deteriorating physical condition. When her symptoms worsened abruptly, she attended and emergency room and was referred to a neurologist, who called to tell me that my patient had multiple sclerosis. The patient was not angry at my oversight and our psychotherapy continued, but its focus shifted from interpreting or ignoring symptoms to adapting and coping with them.

A difficult aspect of biological formulation is the accurate assessment of bodily symptoms in the somatoform disorders, particularly in patients with accompanying medical

conditions. This may call for considerable clinical acumen since the fundamental task is to determine the degree to which disability is disproportionate to known organic disease (Blackwell and Gutmann 1987). Neurologists and internists make this diagnosis on the basis of discrepancies or inconsistencies between signs or symptoms and the known pathophysiology of the condition, but psychiatrists have the added responsibility of eliciting what primary or secondary gain exists to amplify suffering beyond what disease can account for. What irreconcilable conflicts or irresistible rewards have driven or seduced the patient into the sick role? A 52-year-old, devout, Catholic Puerto Rican mother of two teenagers developed a relatively rapid onset paraplegia for which the neurologists could find no organic cause. Careful history taking revealed the symptoms began 24 hours after her 15-year-old daughter announced she was pregnant and one week after her son was arrested for dealing drugs. Her husband, from whom she was separated, had returned home to help deal with the family crises and had assumed all household responsibilities as a result of her sickness. The presence of such dynamics, however, should not blind us to the fact that fully a quarter or patients diagnosed as conversion disorder subsequently develop a physical condition (Watson and Buranen 1979).

Whatever our hopes for the biological revolution in psychiatry, we remain far more heavily dependent than the rest of medicine on history taking. However, examination and investigation are becoming increasingly important and contributory to formulation.

Examination includes both the patient's physical condition and mental status. Psychiatry still suffers from the psychodynamic excesses of the 1940s and 1950s when our specialty abolished the internship and espoused a "hands off" approach to evaluation. As part of the tragic error of "demedicalization," as recently as 1975 only 7% of psychiatrists believed that physical examination was indicated or useful (McIntyre and Romano 1975). However, of those who did their own physical examination, 94% found them useful in establishing the diagnosis. Even today the task of examining the patient physically on admission to the hospital is still too often delegated to unlicensed physicians or moonlighting medical students who may have little understanding of how occult physical illness can cause or aggravate the patient's mental condition. This absurd dualism will continue as long as our training programs perpetuate it. Recently I evaluated an elderly man about to be discharged to a nursing home with a treatment refractory retarded depression. The internist who admitted him had missed the significance to his

slow pulse, sluggish reflexes and dry skin. The psychiatrist who treated him unsuccessfully with antidepressants had overlooked the abnormal thyroid function test. After correction of his thyroid status and treatment with ECT, the patient's condition improved significantly and he was again able to care for himself.

Equally important are the nuances of the mental state that may indicate a biological component. These are mainly those impairments of cognitive function in orientation, memory and judgement that can be elucidated by the Mini-Mental State Exam (Folstein et al. 1975). Because fluctuations in mental state are a cardinal feature of organic impairment, it is often useful to examine the patient more than once (especially in the evening when "sun-downing" occurs) and to obtain information from the patient's relatives of care providers.

It is especially important for the psychiatrist to be aware of the cognitive and emotional changes that may be related to structural lesions in the brain (Solomon and Masdeu 1989). On occasion, particularly early in the disease process, these may provide important clues to localization or etiology. Lesions of the frontal lobe (Ron 1989) are especially prone to present in an insidious manner that may mimic psychiatric disorder, resulting in delayed surgical intervention, sometimes with tragic consequences.

In addition to history taking and examination, laboratory tests and investigations may also contribute to biological formulation in two ways. First, they help reveal or exclude concurrent medical conditions that may be causing or contributing to changes in mental status. Second, they may provide diagnostic confirmation of the psychiatric diagnosis itself. Precisely what tests are ordered should certainly be influenced by such factors as the patient's age, symptomatology, medical history and proximity of previous physician visits. It is customary to include urinalysis, a complete blood count (including folate and vitamin B12 levels) and tests of hepatic, renal and thyroid function. Electrolytes, blood glucose, a toxic screen (for drugs or alcohol) and syphilis serology are also important. Coupled with a chest X ray and physical examination, such a panel is usually adequate to rule out the majority or potential underlying organic conditions or to reveal the more common toxic, metabolic or nutritional causes for a delirium. An interesting challenge to indiscriminate broad-scale laboratory tests (White and Barraclough 1989) found that only thyroid function tests (in women), urinalysis (in women), white cell counts and syphilis serology were justified by frequency of abnormal results.

Obviously, the quality of primary medical care in the population screened is significant and it would be unwise to extrapolate such results from one culture (in the case Britain) to all other cultures, particularly when medico-legal considerations may be operative (as is true in the United States). An electroencephalogram may also be helpful in the diagnosis of protracted delirium or in revealing epileptiform processes that sometimes contribute to psychoses. Computed tomography or MRI provide clinicians with increasing specificity in the diagnosis of dementia and neuropsychological testing may be valuable in the localization or cortical lesions.

In today's cost-conscious climate, clinicians should be aware of the criteria for imaging techniques (Weinberger 1984). There is increasing evidence that MRI may reveal more detailed and specific pathology than CT in some conditions (Jordan and Zimmerman 1990). Of special interest to psychiatrists is the finding of subcortical white matter lesions in various forms of psychosis (Colon et al. 1990; Miller et al. 1989). Recently, my colleagues and I investigated three elderly patients with late-onset paranoid delusions who had relatively intact cognition. Each had an abnormal MRI that showed subcortical encephalopathy. Although this may be a chance finding between a common clinical symptom and a new sensitive test, it illustrates the exciting possibilities that new techniques may offer in understanding etiology and enhancing diagnosis.

More specific neuroendocrine tests such as dexamethasone suppression or thyrotropin-releasing hormone stimulation are probably best reserved for those treatment-refractory cases (Zohar and Belmaker 1987) where it may be helpful to establish an organic basis for the condition before initiating more aggressive treatment strategies, such as ECTor combination chemotherapies.

Finally, it should be remembered that an increasing number of patients with AIDS may present initially with a psychiatric syndrome (King 1990). The central nervous system manifestations of this condition are as protean as those due to syphilis in an earlier era. Human immunodeficiency virus testing with appropriate confidentiality may therefore be indicated, particularly in individuals who are members of at-risk populations.

Treatment and Prognosis

Biological features may also influence choices of treatment and prognosis. Drugs are not equally effective across the spectrum of Axis I disorders; biological agents are most likely to exert benefit in those conditions with most evidence for a biochemical etiology (Blackwell 1975). Disorders that can be provoked by chemical means may benefit from them. Reserpine can cause depression, amphetamine can cause a reactive psychosis indistinguishable from schizophrenia and lactate infusion will induce panic attacks. Benefit derived from drugs in these disorders is due to their specific biochemical action (as opposed to change because of placebo response or spontaneous remission). These two latter sources of improvement are ubiquitous but variable with regard to diagnosis. A finding from controlled studies is that patients with obsessive-compulsive disorder show virtually no placebo response, so that although benefit from the active agent is seldom dramatic and often incomplete, it is always specific (Thoren et al. 1980). The elderly, on the other hand, who may be isolated and lonely, often display a large nonspecific response to low dosages of safe drugs that are little more than rational placebos. Patients with medical conditions tend to respond poorly to antidepressants, are often sensitive to side effects and show little specific or nonspecific improvement. The use and outcome of medications in personality disorders are colored by the condition. Dependent patients may be difficult to wean; aggressive people may become disinhibited; and borderline patients will react to drugs as they do to people, with alternating idealization (a wonder drug) or disparagement (terrible side effects).

Beyond these broad generalizations, psychiatry finds itself at a disadvantage relative to the rest of medicine. There is no solid evidence for treatment specificity when selecting among drugs in a particular category to treat a defined Axis I disorder (Paykel 1989). For example, all antidepressants, irrespective of their mechanism of action, are equally effective and attain a comparable 70%-80% good outcome when given to a large, heterogeneous group of depressed individuals. The search for a specific responder to monoamine oxidase inhibitors (MAOI) has lasted for 30 years with results similar to the search for the Loch Ness monster—reliable observers report infrequent sightings but each describes something different (Blackwell 1986). More confusing still is the fact that drugs called antidepressants can benefit diverse conditions, such as chronic pain, enuresis and panic disorders, often independent of a consistent improvement in affect (Blackwell 1987).

Faced with this lack of treatment specificity relative to the clinical syndrome, the choice between drugs is often influenced by other features of a disorder. The most reliable is a history or response to a particular drug in a previous episode; not only may this predict the degree or response but also its rapidity and completeness. Less often available and supported by slender research literature is the notion that the response of blood relatives may predict benefit in a proband. Recently, I treated a young woman with an atypical bipolar disorder who responded well to lithium after 10 years of chaotic life on the streets. When her mother witnessed the improvement, she insisted that her husband, who had been treated for years with phenothiazines at another institution, also receive lithium. He, too, obtained considerable benefit and both father and daughter, who share similar clinical conditions, are now well stabilized.

A second avenue of influence on choice between biological interventions is the need to match the side effect profile of the drug to the susceptibility of the patient. An elderly man with a large prostate may develop urinary retention on a sedative tricyclic compound; an older woman placed on phenothiazines may begin to display parkinsonism. The elderly in general are vulnerable because of their altered metabolism, concurrent medical conditions and other medications with which psychotropic drugs may interact (Raskind and Eisdorfer 1978). At times, ECT may be the safest option for such patients.

Choice among medications is also dictated by the experience of the practitioner and the logic that underlies sequential exposure to different drugs. “First-choice” medications have the seductive property of reinforcing the prescribing prejudice of the practitioner, since spontaneous remission and placebo responses are added to the specific pharmacologic benefit (Blackwell and Taylor 1967). Subsequent exposure of treatment-refractory patients to second-choice agents or augmentation protocols often follows the law of diminishing returns. An ideal “first-choice” drug is one that does not hamper subsequent treatment if it fails; fluoxetine (with its lengthy half-life) and MAOI (with their prolonged enzyme inhibition) have obvious drawbacks. A major contribution of biological treatments to psychiatry has been the methodology of controlled trails, which can protect us from the referral biases and self-fulling prophesies of our own practice (Paykel 1989). Biological formulation is informed by the research literature as well as by individual experience.

Except on those occasions when they facilitate diagnosis, special investigations and laboratory tests provide little guidance for treatment choice in psychiatry. An exception is the use of plasma level monitoring for those drugs whose bioavailability and metabolism make such information useful in determining compliance, the adequacy of treatment or its relationship to adverse effects (Kirch 1989). Lithium treatment and prophylaxis is undoubtedly the best example, but the use of blood levels may also be valuable in high-risk populations or treatment-refractory patients in whom the need to titrate medication carefully can dictate choice of a drug (such as nortriptyline) where there is a reasonably reliable relationship between plasma levels and outcome. Monitoring for blood dyscrasia is also routine in the use of carbamazepine and clozapine.

While prognosis is a part of formulation, it is a most uncertain art. In some of the brief reactive or schizophreniform psychoses, good outcome is linked to rapid onset, clear psychosocial precipitation and affective features. In general, however, the heterogeneity of even our major classifications (Bleuler's "group of schizophrenias") and the multiplicity of biopsychosocial factors almost guarantee an unpredictable natural history in any individual, although it is true that controlled trials provide statistical blueprints within which to speculate about outcome. The likely length of any biological treatment is logically related to the natural history of the untreated and underlying biochemical condition (Blackwell 1975). But we have had biological treatments since the mid-1930s and effective drugs since the mid-1950s, so it is difficult to find untreated populations that will provide yardsticks. Age at onset, severity of symptoms, comorbidity, previous episodes and psychosocial stressors may all enter the predicative equation, but often we have only a stereotype of good prognosis that applies to all interventions, biological or otherwise. Those likely to do well have a good premorbid personality; occupational, marital and social stability; and a clear onset related to a defined precipitant. Nowadays one hardly need to add that such individuals are more likely to have good insurance. A counterpoint to the uncertain prognosis in psychiatric patients is that medical residents who rotate through our inpatient services express surprise at the good response of psychiatric patients to medications compared with the chronic treatment-refractory patients they commonly encounter on medical floors.

The Case of Mr. A

The formulation of the case of Mr. A is presented in two stages: first, a lengthy exposition that illustrates components with their underlying logic and second, a pithy succinct synopsis that provides the essence of a model formulation.

Case Summary

Mr. A is a 42-year-old businessman who presents with complaints of loss of interest in his job, hobbies and family over a period of six weeks. He acknowledges periods of profound sadness, reduced appetite with significant weight loss, insomnia, fatigue and recurrent thoughts of death, but denies suicidal ideation. He denies any precipitants but does admit that his expected job promotion has not materialized.

Mr. A describes himself as unusually serious, conservative and relatively unable to express affection. He also acknowledges trying to be perfect, needing to be in control of every social situation and having an excessive commitment to work.

Mr. A indicated that his marriage has been worsening for several years and describes his wife as flighty, overemotional and helpless under stress. For the past several years, she has been angry and distant and has declined to be involved sexually with him. Since the onset of his symptomatology, however, she has been solicitous and obviously concerned. The A's have two children, a 12-year-old girl and a 10-year-old boy, who appear to be doing well at school and at home.

Mr. A describes his family origin as very poor. His father deserted his mother when the patient was 12-years-old; as the oldest child, he had to take considerable responsibility for younger siblings, as well as to work part-time while attending school. Mr. A's maternal grandfather committed suicide and two maternal uncles were alcoholic. A paternal uncle died in prison after a long period of antisocial behavior.

Physical, laboratory and neurologic studies are negative. The DMS-III-R multiaxial diagnosis is as follows:

Axis I Major depression, single episode (296.22)

Axis II Obsessive-compulsive personality disorder (301.40)

Axis III No relevant current physical disorder

Axis IV Severity of Psychosocial Stressors: 3, with moderate stress due to marital discord.

Axis V Current Global Assessment of Functioning (GAF) score: 52;

highest GAF score past year: 67

Explanation

Mr. A's family history suggests a genetic predisposition to affective disorder, both directly on the maternal side with his grandfather's suicide and indirectly by comorbidity with alcoholism and sociopathy in uncles on both side of the lineage. Other potential etiologic factors that need to be excluded by further history taking include the absence of physical illness or the use of any medications and abuse of recreational drugs (particularly cocaine) or alcohol. In addition to facts obtained by history taking, these possibilities should be pursued with information from the patient's primary care practitioner and another family member who knows Mr. A's habits well. The negative results of the routine panel of laboratory tests (presumably including thyroid function) would also help rule out any biological factors contributing to etiology.

Description

Two aspects of the illness itself support biological formulation. The onset is relatively abrupt and marks a clear-cut change from a customary level of function. Second, there are features suggestive of melancholia that are often attributed to hypothalamic dysfunction. These include insomnia, weight and appetite loss and anhedonia. Not mentioned, but to be inquired about, would be any changes in his sexual interest or activity (inside or outside the marriage).

Treatment and Prognosis

Outpatient treatment would be indicated by continued ability to work, absence of suicidal ideation and support and involvement by his wife in medication management

Since there are no previous episodes of illness, no family members treated for depression and no concurrent physical illnesses or medications to influence treatment, the choice of an antidepressant would be dictated by need for some sedative properties to deal with Mr. A's

insomnia. A tricyclic compound such as nortriptyline, imipramine or amitriptyline would be selected, any of which could be subsequently monitored by plasma levels if response is problematic or if serious side effects occur. Before initiating treatment, discussion with Mr. A would determine his attitudes, beliefs and concerns about the appropriateness of medication. Given his obsessional personality characteristics, some concern about the possibility of drug dependence might be anticipated. On the other hand, it is also likely that he would not be particularly psychologically minded and that an explanation based on a possible chemical imbalance would be appealing to him. Assuming Mr. A's concurrence with treatment, the benefits, side effects and time course of response to medication would be explained. Immediate improvement in sleep would then be predicted, to be followed by more insidious uplift in mood. A relatively low starting dosage would be given two hours before bedtime and titrated upward in small increments to obtain 6-8 hours of restful sleep with tolerable side effects. This dose would be maintained unless the predicted improvement in melancholic symptoms did not occur after 2-3 weeks, in which case the dose would be further escalated.

The prognosis given Mr. A would be good for this episode and somewhat more guarded for future affective illness. Of 10 individuals, seven or eightrespondwell to antidepressants, and Mr. A's history reveals several good prognostic features, including melancholia, a good premorbid personality and a high level of social and occupational function. With affective illness, 50% manifest as a single lifetime episode, but future relapses would be more likely if etiologic factors remain unresolved. Both the duration of drug treatment and likelihood of future relapses might therefore be related to the extent to which concurrent psychotherapy (psychodynamic or behavioral) and social change (e.g., divorce or job change) occur.

The average length of an untreated first episode of depression was about 6-8 months before there were effective treatments. Mr. A would be told that medication should be continued for at least this time period and that cessation of drug therapy would also depend on the extent to which life stress was reduced and his coping capacity had improved. When these criteria were attained, medication would be slowly weaned over 2-3 weeks to avoid withdrawal and treatment would be terminated after a further month or so of drug-free well-being.

The formulation of the case of Mr. A merits a final word of caution and comment that incorporates explanatory, descriptive and treatment implications. Mr. A may invite the same kind

of single-minded error illustrated in the Osheroff case (Klerman 1990; Stone 1990). Personality quirks are common and nobody's life is free of blemish or painful incident. In this instance, the outstanding feature of the case is not the presence of such everyday occurrences, but the onset for the first time in mid-life of a new, severe and incapacitating condition with no clear-cut cause. In the past, such illnesses were often considered "endogenous" and were typified by their rapid and complete resolution with biological treatment alone. It is distressingly simple to construct a web of psychodynamic speculation and, in doing so, to be seduced into withholding drugs while the patient is encouraged to "work through" his or her imagined predicament. Worse still, drugs may be pejoratively viewed as "trivializing the illness experience" or "stifling affect," with recovery dismissed as a "flight into health." Mr. A deserves better, and although he may benefit in the long term from psychological insights, he should never be denied psychotropic medication. The clinical criteria for different types of psychotherapy (cognitive, psychodynamic or interpersonal) in depression have been well described (Karasu 1990), but it should be remembered that drugs alone would be the treatment choice in some cultures, that even if combined with psychotherapy they make the major contribution to variance in outcome for Mr. A's type of illness and, finally, the rules of parsimony suggest that the simplest, most effective treatment be offered first.

The Biological Formulation

This 42-year-old married, white father of two has experienced a 6-week onset of his first episode of major depression characterized by melancholic features but without suicidal ideation. The family history is positive for affective disorder and comorbid conditions, but there are no other biological predisposing factors. Outpatient therapy with a tricyclic antidepressant is predicted to produce an excellent response based on good prognostic features, including premorbid personality and relative social stability. Prognosis for future episodes is more guarded and may be influenced by response to psychological interventions and social change.

Summary and Conclusion

In this chapter we have considered biological formulation from several perspectives. First, we examined the degree to which technological advances as well as social and philosophical change have contributed toward a paradigm shift that attributes increasing

significance to the biological understanding of psychiatric disorders. Next, we reviewed the extent to which existing knowledge supports the four basic hypotheses on which a biological contribution may be assumed. Finally, the way in which such knowledge is put to use in making a formulation has been discussed, both in general terms and then in specific relationship to the case of Mr. A.

Diagnostic Illusions

OED: *illusion;* a deceptive appearance or impression; a false belief or idea.

Via: OFr from L, *"illudere,"* to mock.

Until the mid-20th century psychiatric disorders were seldom, if ever, based on the response to a treatment; there were none - beyond those stifling selected symptoms (barbiturates, bromides, chloral, amphetamine, paraldehyde, etc.).

Instead, classification of disorders was based almost entirely on clinical features of presumed etiology (familial, environmental or "endogenous"), nosology, natural history, prognosis (the mark of a good clinician) and outcome. Notable systems were defined by Kraepelin, Schneider, Wernicke- Kleist and Leonard (WKL) among others less well accepted.

The discovery of effective remedies in mid-20th century and after (1949-1974) sparked interest in a putative connection between particular drugs and specific disorders. A flock of diagnostic systems evolved in rapid succession: The ICD (UK), the DSM (USA), prototypes (French), neuro-pathologies (German), CODE (Ban), selective neurotransmitters (NIH), genetic diathesis (universal) and RDoC (NIMH). The hard-earned clinical knowledge accumulated before this "golden era" was soon abandoned and, to all intents, disappeared from educational programs and clinical practice.

In 1980 DSM III and clinical consensus based primarily on symptoms became America's ideal, a perpetual source of revenue for the American Psychiatric Association (APA) but also

popular worldwide. The multiaxial system allowed for attention to social and psychological features of illness, but these were rapidly subordinated to Axis 1 presumptive biological disorders often for insurance purposes but also manipulated by industry to define syndromes that inflated drug use and revenue - part of which was employed to suborn prominent members of the psychiatric profession as their shills (OED: *shill;* an accomplice, a hawker, gambler or swindler, an enthusiastic customer to entice others).

With limited exceptions, sloppy diagnosis, Big Pharma's hegemony and NIMH ambivalence have defiled the latest of many diagnostic systems with nothing ready to replace it. Our ignorance of how the brain translates treatment into outcomes remains a profound mystery. The brain guards its secrets well.

References:

American Psychiatric Association: Diagnostic and Statistical Manual: Mental Disorders. Washington, DC, American Psychiatric Association. 1952.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 2nd Edition. Washington. OC. American Psychiatric Association, 1968.

American Psychiatric Association: Diagnostic and Statistical Manual of MentalDisorders, 3rd Edition. Washington. DC, American Psychiatric Association, 1980.

American Psychiatric Association: Diagnostic and Statistical Manual of MentalDisorders, 3rd Edition. Revised. Washington. DC, American Psychiatric Association. 1987.

Andreasen NA (ed): Brain Imaging: Applications in Psychiatry. Washington. DC, American Psychiatric Press, 1989.

Ayd FJ: The impact of biological psychiatry, in Discoveries in Biological Psychiatry. Edited by Ayd FJ, Blackwell B. Baltimore, MD, Waverly Press, 1984, pp 230-243.

Ayd F, Blackwell B (eds): Discoveries in Biological Psychiatry. Baltimore, MD,Waverly Press, 1984.

Baker NJ, Berry SL, Adler LB: Family diagnoses missed on a clinical inpatientservice. Am J Psychiatry 144:630-632, 1987.

Blackwell B: Rational drug use in psychiatry, in Rational Psychopharmacotherapy and the Right to Treatment. Edited by Ayd FJ. Baltimore, MD, Ayd Medical Communications, 1975.

Blackwell B: Antidepressant drugs, in Meyler's Side Effects of Drugs, Annual 10.

Edited by Dukes MNG. Amsterdam, Elsevier Science Publishers BV, 1986 Blackwell B: Antidepressants as adjuncts in chronic idiopathic pain management.International Drug Therapy Newsletter 22:1-4, 1987.

Blackwell B, Gutmann M: The management of chronic illness behavior, in IllnessBehavior. Edited by McHugh S, Vallis M New York, Plenum, 1987, pp 401- 408.

Blackwell B, Taylor DC: An operational evaluation of MAO inhibitors. Proceedingsof the Royal Society of Medicine 60:8304333, 1967.

Bouckoms A:Letter to the editor. Psychiatric Tunes, May 1990.

Brandt J, Quaid KA, Folstein SE, et al: Presymptomatic diagnosis of delayed-onset disease with linked DNA markers: the experience in Huntington's disease. JAMA261:3108-3114,1989.

Carroll BJ: Dexamethasone suppression test: a review of contemporary confusion.J Clin Psychiatry 46:13-18, 1985.

Conlon P, Trimble MR. Rogers D: A study of epileptic psychosis using magneticresonance imaging. Br J Psychiatry 156:231- 235,1990.

Cooper JE, Kendell RE, Garland BJ, et al (eds): Psychiatric Diagnosis in New Yorkand London. London, Oxford University Press, 1972.

Donovan BT: Humors, Hormones and the Mind: An Approach to the Understandingof Behavior. New York, Stockton Press, 1988.

Fink M: How does convulsive therapy work? Neuropsychopharmacology 3:73-82, 1990.

Folstein MF, Folstein S, McHugh PR: Mini-Mental State: a practical guide for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-194, 1975.

Gershon ES, Merrill CR. Goldin LR. et al: The role of molecular genetics in psychiatry. Biol Psychiatry 22:1388-1405, 1987.

Hall RCW (ed): Psychiatric Presentations of Medical Illness. New York, SpectrumPublications, 1980.

Hunter R, Macalpine I (eds): Three Hundred Years of Psychiatry. London, OxfordUniversity Press, 1964.

Jefferson JW, Marshall R: Neuropsychiatric Features of Medical Disorders. NewYork, Plenum, 1981.

Johnstone L: Users and Abusers of Psychiatry: A Critical Look at Traditional PsychiatricPractice. London, Routledge. 1989.

Jones E: Toe Life and World of Sigmund Freud, Vol 1. New York, Basic Books,1953.

Jordan BD, Zimmerman RD: Computed tomography and magnetic resonance imagingin boxers. JAMA 263:1670-1674, 1990.

Kafka MS, Paul SM: Platelet α2 adrenergic receptors in depression. Arch Gen Psychiatry 43:91-95, 1986.

Kuhn T. The Structure of Scientific Revolution. Chicago, IL, University of Chicago Press, 1970.

Kalinowsky LB: Biological psychiatric treatments preceding pharmacotherapy.In:Discoveries in Biological Psychiatry. Edited by Ayd F, Blackwell B. Balti- more, MD, Waverly Press, 1984, pp 59-f,7.

Karasu TB: Toward a clinical model of psychotherapy for depression, Il: an integrative and selective treatment approach. Am J Psychiatry 147:269-278, 1990.

King MB: Psychological aspects of HIV infection and AIDS. Br J Psychiatry156:151 - 15 6, 1990.

Kirch DC: Medical assessment laboratory testing in psychiatry, in Comprehensive Textbook of Psychiatry. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Williams & Wilkins, 1989, pp525-533.

Klerman GL: The psychiatric patient's right to effective treatment implications of Osheroff v Chestnut Lodge. Am J Psychiatry 147:409-418, 1990.

Lazare A: A multidimensional approach to psychopathology, in Outpatient Psychiatric Diagnosis and Treatment, 2nd Edition. Edited by Lazare A. Baltimore, MD, Williams & Wilkins, 1989, pp 7-16.

Lishman WA: Organic Psychiatry. Longon, Blackwell Scientific Publications, 1978.

Loosen PT, Prange AJ: Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: a review. Am J Pscyhiatry 139:405-412, 1982.

McIntyre S, Romano J: Is there a stethoscope in the house (and is it used)? Arch Gen Psychiatry 34:1147-1151, 1975.

Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR.Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N Engl J Med1990; 322(12):789-794.

SperryL., Gudeman JE, Blackwell B. and Faulkner LR. *Psychiatric Case Formulations*. American Psychiatric Press, Washington, DC,1992.

Szymanski LS, Crocker AC: Mental retardation in Comprehensive Textbookof Psychiatry. Edited by Kaplan HI, Sadock BJ. Baltimore, MD, Williams & Wilkins, 1989, pp 1728-1771.

Thoren P, Asberg M, Cronholm B, et al: Clomipramine treatment of obsessive compulsive disorder. Arch Gen Psychiatry 37:1281-1285, 1980.

Watson CG, Buranen C: The frequency and identification of false positive conversionreactions. J NervMent Dis 167:243-247, 1979.

Waziri R; Book forum. Am J Psychiatry 147:355-356, 1990.

Weinberger DR; Brain disease and psychiatric illness: when should a psychiatristorder a CAT scan? Am J Psychiatry 141:1521- 1524, 1984.

Whalley LJ, Christie JE, Blackwood DHR, et al: Disturbed endocrine function inthe psychoses. Br J Psychiatry 155:455-461, 1989.

White AJ, Barraclough. B: Benefits and problems of routine laboratory investigationin adult psychiatric populations. Br J Psychiatry 155:65-72, 1989.

Zobar J,Belmaker RH (eds): Treating Resistant Depression. New York, PMA Publishing, 1987.

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