The Journal of Mind and Behavior
Summer 2004, Volume 25, Number 3
Pages 213–226
ISSN 0271–0137

Biological Markers: Search for Villains in Psychiatry

Lawrence Greenman

Hudson Valley Health Care System

The article explores the influence of unproven specificity of pathogenesis manifested in clinical psychiatry and research. A selected literature review of studies attempting to identify a biological marker is presented. To date, the search for a biological marker to establish a psychiatric diagnosis has been unsuccessful. Clinical settings and programs are described which seem to be driven by psychological issues, one such example being the search for villains. Thus, specific assumptions about etiology affect therapy technique and treatment planning and may be disadvantageous to patient care. Biological and psychological development in all of its phases is subject to a diverse range of perturbations, intrinsic as well as extrinsic. A flexible, balanced view is called for before specificity is extended to general theories, which, in turn, affect therapy and treatment settings.

Pursuit of the pathogenesis of psychiatric illness has been going on for more than one hundred years. This paper will discuss the notion of specificity in the exploration of psychological and biological determinants of psychiatric disorders. I will present evidence that single etiological causes have been unsuccessful in clarifying the manifestations of mental illness. To support this view, three references are presented to represent psychoanalytical explorations of specific psychogenic determinants of psychiatric syndromes such as schizophrenia and "the neurosis." A more extended review of selected biological studies is then undertaken since, in the past few decades, advances in biological theory and technical procedures have spurred an enormous amount of investigative activity. In particular, the studies of biological markers will be assessed in terms of specificity, outcome, and influence on clinical treatment. The vast majority of psychiatric disorders are the outcome of multiple diverse, and complex determinants (the bio–psycho–social model). Moreover, psychiatric disorders occur at various stages of develop-

The author would like to thank Robert Sobel, M.D. for his insightful comments and valuable guidance in the organization of the manuscript. Requests for reprints should be sent to Lawrence Greenman, M.D., c/o Perrone, 3489 Zurich Court, Carson City, Nevada 89705. Email: lgreenmanmd@msn.com

ment in patients, each patient with a unique history. Studies involving central nervous system (CNS) trauma or degenerative processes will not be here considered. It is my intent to lead the reader to the conclusion that a concentration of effort to identify a single etiological factor as a cause of a psychiatric disorder is misguided and has, in turn, a constrictive influence on clinical treatment.

Psychological Explorations

Before the development of technology to explore the CNS, there were attempts to find single explanations of "mental illness" based on psychological premises that have since fallen by the wayside. Fromm–Reichmann (1948) wrote about the role of the schizophrenogenic mother in the pathogenesis of schizophrenia. Bateson, Jackson, Haley, and Weakland (1956) developed the "double bind" hypothesis, which involved a specific type of a communication problem by an important family member, typically a parent. In his discussion of the theories of pathogenesis Arlow (1981, p. 499) referred to the "quest for the villain" to explain the etiology of mental illness. He specifically cites the notion of demonic possessions and describes variations of this concept in psychoanalytic terms to account for the etiology of neurosis.

> The villain has taken many guises in the course of the history of psychoanalysis — the older brother who seduced his sister, thereby arousing her sexuality prematurely and causing her to have hysteria (justice triumphed, at least partially, since the older brother paid for his crime in the early days by developing obsessional neurosis); the nurse who threatened the masturbating little boy that his fingers would be cut off; the overbearing implacable father whose terrifying demeanor forbade identification with him or the phallic mother; the thoughtless parents who took part in the primal scene spectacle; down to our time of preverbal pathogenesis where crime, now wordless, is perpetuated by the current version of the villain, the unempathic or less than adequate mother. (p. 500)

I maintain that the contemporary focus on identifying a biological marker is reminiscent of Arlow's description of the quest for a villain in psychoanalysis. During the period in which psychoanalysis held sway in academic psychiatry, there was a focus on personalities and events in a patient's past to identify a psychogenic etiology of psychiatric disorders. Since the expansion of biological psychiatry, there has been a focus on finding a biological marker, which would (presumably) be associated with a specific biological etiology of a psychiatric disorder. Although each focus of study shares the notion of specific etiologies of mental disorders, the one-dimensional approach is pursued to the neglect of the other. From my point of view, as it relates to the shift from the psychoanalytic to the biologic, there has been a corresponding displacement of objects from personified entities to biological entities. Of course, psychological factors or biological dysfunction play contributing etiological

roles, in varying proportions, in the development of psychiatric disorders. I merely want to emphasize that the development of a psychiatric disorder is derived from a complex interplay of etiological factors. In order to support my view that the quest to find a biological entity turns out to be as unrewarding as the quest to find a personified entity as a specific factor in causing a mental illness, I have selected representative scientific studies which span the last thirty-plus years and at some point were or are given serious consideration. The studies have clearly yielded both negative and positive findings. Certainly, a great deal of scientific biological specificity is presented. However, specificity of data generated in the study of psychiatric disorders, even if the data are positive, does not indicate etiological specificity of a disorder. In an effort to avoid misrepresentation, I present the authors' conclusions to their respective articles, for the most part, in their own words. The studies address a wide spectrum of psychiatric diagnoses and are selected from three categories frequently used in biological research.

Biological Studies

Studies Which Have Attempted to Find a Biological Marker in Urine, Blood, or Electrical Tracings

Siegle and Tefft (1971) reviewed more than fifty papers in which the "pink spot" 3,4-dimethoxyphenylethylamine was examined in the urine of schizophrenic patients as a marker for schizophrenia and was not validated. According to Stabenau, Creveling, and Daly (1970) however, the pink spot found in urine was derived from an exogenous plant source, common tea. Another approach involves EEG and computerized EEG tracings of schizophrenic patients in an attempt to detect specifics of the tracings, which would differentiate the former from non-schizophrenic patients. Focal EEG changes induced by anti-septal bodies were assessed by Garey, Heath, and Harper (1974) to identify chronic schizophrenia in 100 patients versus 100 matched normal volunteers. The findings of the study, however, remain mixed. Itil, Marasa, Saletu, Davis, and Mucciardi (1975) went so far as to suggest "computerized EEG may be helpful in selecting the best drug for a particular patient . . . and may help to monitor drug treatment and daily dosages" (p. 200). Yet, this treatment method has been left by the wayside due to a lack of confirmed clinical correlations. Fleming (1994) reviewed studies of REM and non-REM sleep in psychiatric patients and concluded "No single sleep variable, particularly REM latency, is sensitive or specific enough for diagnosis of any psychiatric disorder, especially depression" (p. 335). Heath, Guschwan, and Coffey (1970) studied immunoglobulin (IgG) in the blood serum of schizophrenic patients. The authors concluded, "the many variables involved prevent us at this stage of our investigations to

substantiate our contention that schizophrenia is probably a single disease entity" (p. 395).

Studies Which Attempt to Assess Hormones, Metabolites, and Neurotransmitters in Efforts to Find Biological Markers

A relationship between dysthymia and two putative biological markers of affective illness was explored by Ravindran, Bialik, and Lapierre (1994). Platelet monoamineoxidase activity and the dexamethasone suppression test were the hypothesized biochemical correlates of the therapeutic response of fluoxetine in dysthymic patients. The findings of the study "support the view that there is a biologic substrate for some sub groups of dysthymia. This biological component may involve the hypothalamic pituitary adrenal axis and serotonergic systems" (p. 111). The leap from findings to conclusions is, perhaps, overstated and has not stood the test of time. Moreover, the complex and central biological component, the hypothalamic pituitary adrenal axis, is also involved in other psychiatric disorders. Mazure, Quinlan, and Bowers (1997) explored recent life stressors in 34 admitted psychotic patients for association with four biological markers of stress. The markers examined were plasma cortisol, the serum prolactin, plasma free homovanillic acid and plasma free methoxyhydroxyphenylethyglycol. Mazure et al. concluded that "Of the biological variables examined only pretreatment admission serum cortisol was correlated with stressor severity" (p. 865). A rather small yield of correlation from a large pool of markers.

Smith, Dewey, Brodie, Logan, Vitkun, Simkowitz, Schloesser, Alexoff, Hurley, Cooper, and Volkow (1997) used Position Emission Tomography (PET) to measure the neurotransmitter serotonin in normal human subjects. The studies used a radiotracer for the D2 receptor, and a pharmacological challenge with a serotonin-releasing agent and re-uptake inhibitor, fenfluramine, in 11 normal male subjects. Plasma levels of fenfluramine, norfenfluramine, homovanillic acid, cortisol, and prolactin were determined. The authors concluded that "the study of serotonergic modulation of dopamine function has implications for etiologic and treatment mechanisms in several neuropsychiatric disease states, including schizophrenia, affective disorders, obsessive–compulsive disorder, and substance abuse (e.g., cocaine dependence)" [p. 495]. Here, again, none of the imputed implications of such a broad sweep across psychiatric diagnostic categories has been worked out in a clinically relevant way. The significance of the study, therefore, remains questionable at best. Of course, it may be that specific biological substrates do not necessary translate into specific etiologies of psychiatric disorders. However, the burden of demonstrating the connection between biological data and clinical entities rests with the researchers. The complexities and inter-relatedness of neurobiological systems is by itself formidable. Importantly,

and often overlooked by biological researchers, the psychological component is inextricable from the biological component. The mind, after all, is housed in matter — even in derived biological data analyzed with complex statistical methods.

Brain Architecture Has Been Meticulously Explored in Attempts to Identify Biological Markers

The technique of radioactive imaging is frequently used in biological studies of the CNS. Symonds, Olichney, Jernigan, Corey–Bloom, Healy, and Jeste (1997) reported on MRIs of sixty-nine patients, 30 were with early-onset, 24 with later-onset schizophrenia, and 15 with "other psychosis," as compared with 41 non-psychotic individuals. "There were no significant differences between psychosis patients and normal comparisons . . . or between early-onset and late-onset schizophrenia-related disorders in frequency, type or severity of gross structural abnormalities" (p. 251). Thus, radioactive imaging was unable to identify a biological marker of gross structural abnormality in the brains of "psychotic" patients.

Fried (1972) hypothesized that the septal region of the brain was linked to an immunological etiology of schizophrenia. Wolf, Hyde, and Weinberger (1994) considered malformations of the septum pellucidum via neuroimaging and suggested that "The increased prevalence of developmental abnormalities of forebrain structures in patients with schizophrenia suggests that dysgenesis of these may be contributing to the neurobiology of schizophrenia and other psychotic disorders" (p. 140). However, neither structural abnormalities of the septum pellucidum nor immunological malfunction has been validated with schizophrenia. Vogeley, Schneider–Axmann, Pfeiffer, Tepest, Bayer, Bogerts, Honer, and Falkai (2000; see Lewis, p. 1) found that the "gyrification index, a measure of cortical folding, [was] significantly higher than normal, by an average 7% in the right prefrontal cortex of male subjects with schizophrenia." Lewis (2000, p. 1), in an editorial comment on the Vogeley paper, noted that "However, [Vogeley et al.] also raise the questions of how such abnormalities in different brain regions are related to each other and how they actually contribute to the clinical phenomena of schizophrenia." In other words, the study identified statistically different biological measurements which, however, are inconclusive as markers for schizophrenia.

Raine, Lenez, Bihrle, Casse, and Colletti (2000) attempted to find a biological marker for antisocial personality disorder patients (ADP) and concluded that "these findings provide the first evidence for a structural brain deficit in ADP. This prefrontal structural deficit may underlie the low arousal, poor fear conditioning, lack of conscience, and decision-making deficits that have been found to characterize antisocial, psychopathic behavior" (p. 119). But Damasio (2000) in his commentary on the Raine study believed that

judgment to be forced: "It would not be prudent to conclude from this study and from previous neurobiological studies that inappropriate social behavior is solely a consequence of prefrontal dysfunction caused by acquired lesions or a consequence of structural and functional defects caused by genetic factors, development factors or both. The normal pathological effects associated with that certain area can be properly understood only in the context of multicomponent neural systems" (p. 129). Damasio's cautionary comment may apply as well to so-called overview studies as described in the next section.

Overview Studies

Koyama and Yamashita (1992) summarized a WHO multi-center study in which 543 depressed patients and 246 controls were compared. Biological markers examined were the dexamethasone suppression test, imipramine platelet binding, sleep EEG, ocular potentials and melatonin, serotoninergic functions, and brain imaging. The authors concluded that "It is hoped that 20 studies in markers of depression, which were reported at the 17th CINP Congress, 1980, *may provide in their further investigations* certain biological markers of depression useful for the diagnosis and evaluation of therapeutic effects of depressive illness" (p. 795, my italics). Nonetheless, the CINP Congress failed to define a biological marker for depression. Szymanski, Kane, and Lieberman (1991) also attempted to assess biological markers for schizophrenia: abnormalities in eye movements, electrodermal activity, event-related brain potentials, attention and information processing, and brain imaging. They concluded that ". . . no single possible marker appears specific for schizophrenia. Sufficient evidence does not exist to support the inclusion of biological markers among the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–IV) criteria for schizophrenia" (p. 99). A review of 48 studies was undertaken by Aylward, Harris, Hoehn–Saric, Barta, Machlin, and Pearlson (1996) to assess Obsessive Compulsive Disorder (OCD) and its relation to the function of the caudate nucleus. The authors found that "Although theories of OCD suggest a dysfunction of the caudate nucleus, the structural and functional neuroimaging literature has not consistently verified this" (p. 577). Gonzalez, Cousins, Doraiswamy, and Murali (1966) reviewed the neurobiology of the chronic fatigue syndrome (CFS) and surmised "Given the symptomatology of the data from recent studies, the CNS most likely plays a role in CFS pathology. However, it remains to be shown whether the CNS abnormalities are the cause, result or mediator of CFS patients' symptoms and the degree to which such involvement influences the outcome or prognosis of CFS" (p. 749). In a summary of brain imaging studies, Brodie (1996) concluded that "years of the application of functional brain imaging to the study of psychiatric conditions . . . have resulted in speculative musings,

rather than the construction of a significant, testable hypothesis and validation with an independent sample" (p. 145). Brodie further maintained that "While modern imaging techniques offer an extraordinary set of tools to examine brain–behavior relationships, we must acknowledge uneven success at addressing problems of interest to the clinical psychiatrist" (p. 147).

Petty (1999) posted 227 references in his exhaustive review of structural asymmetries of the human brain associated with disturbance in schizophrenia. He maintains that "disturbances in symmetry are particularly striking in patients with schizophrenia and perhaps all psychotic illness, and may provide the neurological substrate for the etiology and clinical manifestations of the illness" (p. 125). In Petty's view, "structural and functional asymmetries and particularly their integration with clinical measures, still have much to teach us about schizophrenia" (p. 130). However, yet to be established is a direct link between brain asymmetry and the diagnosis of schizophrenia. Gruzelier (1999) referenced 228 citations in his review paper on functional neuropsychophysiological asymmetry in schizophrenia. He concluded,

> In reviewing the neuropsychophysiological evidence of functional asymmetry it is proposed that schizophrenia is characterized by greater disposition of leftward and rightward asymmetries. Central to these is lateral imbalances in the thalamo–cortical and callosal arousal systems, while centrality in schizophrenia follows evidence of reversals in symmetry with changes in symptom profile, clinical recovery, and neuroleptic treatment . . . . It is proposed that the asymmetries arise from endogenous influences of genes, hormones, and early experience including stressors on nonspecific thalamic system asymmetry, and these underpin approach/withdrawal behavior that is manifested in temperament, personality, and clinical syndrome, and which precedes language development. (p. 91)

Further, Gruzelier maintained that "The functional and dynamic nature of the syndrome related asymmetries hold out the hope for medications, not only by neuroleptics, but also by other behavioral, neurophysiological, and neurochemical methods" (p. 110). However, he did not offer any protocols to attempt to establish a connection between his findings and clinical syndromes nor did Gruzelier elaborate on the treatment methods to which he referred. Gur and Chin (1999) examined 38 studies involving 1,169 (schizophrenic) subjects that examined brain laterality via functional neuroimaging and concluded that "the results implicate abnormalities in left hemispheric activity" (p. 141). The authors went on to say that "within this framework, laterality provides a hypothesis that seems to be sustained when examined rigorously. Its [laterality] specific shape and its distribution along other brain dimensions such as cortical–subcortical and anterior–posterior remain to be systematically elucidated" (p. 152). The stated "implications" of a biological abnormality remain to be connected with the clinical syndrome of schizophrenia.

Wright, Rabe–Hesketh, Woodruff, David, Murray, and Bullmore (2000) performed a meta-analysis of regional brain volume and incidence of schizophrenia. The authors analyzed 58 studies which included 1,588 independent patients.

> In summary, this meta-analysis demonstrated global structural differences between patients with schizophrenia and non-schizophrenia comparison subjects: cerebral volume was smaller and total ventricular volume was greater. Regional volume reductions in excess of these global differences were particularly marked in the bilateral medial temporal lobe regions. A general theory of the structural pathology of schizophrenia will need to explain both a complex pattern of cerebral changes and ventricular changes with a different spatial distribution. (p. 23)

The biological findings are specific but the authors look to future studies in the hope of defining a general theory of structural brain pathology.

The distilled truth is that in spite of an enormous accumulation of biological and clinical data, a psychiatrist today is not in a position to order a biological test to diagnose a psychiatric disorder. Indeed, researchers themselves have to establish a diagnosis by other means before a patient is entered into a psychiatric research protocol. The concept of single etiological specificity influences clinical treatment and seems to be associated with the search for biological markers. Support for this view will be given in the following discussion section. I will describe clinical situations I have observed directly or in the literature which have given me cause to reflect upon the deleterious consequences of the unproven hypothesis of a biological marker.

Discussion

As has become evident, the search for biological markers for psychiatric pathology has not yet borne fruit. My impression is that the overwhelmingly detailed neuroanatomical terminology or complicated neurophysiological processes seem to obscure the lack of a conclusion to validate the identification of a biological maker. Yet, that pursuit will undoubtedly continue for a number of reasons: the human need to have simplicity and coherency; the forces of market economics preferentially funding biological studies; and the development of new technologies to invite further exploration. Human behavior is not of course necessarily reducible to pure biology; it is conceivable that given the aforementioned factors this conclusion may never be reached. Perhaps the quest is worthwhile, nevertheless, in that it may yield important findings along the way. However, I find it of great concern that, thus far, the failure to confirm a biological marker has not dispelled the illusion that markers do exist and interventions and thinking based on false presumption have found their way into psychiatric practice. I will discuss four

clinical issues which seem to be related to that false assumption. They are respectively, (1) deinstitutionalization, (2) medical school influence, (3) specificity and constraint of therapeutic options, and (4) polypharmacy and psychotropic regimens.

1. The appeal of the simplicity of a biological marker with its imputed psychotropic drug intervention has, in my opinion, contributed to the mass deinstitutionalization efforts of the late 1950's. The policy of deinstitutionalization failed to take into account the full complexity of schizophrenia and other serious mental illnesses and provided for managing only one dimension of illness(es). As a consequence, significant imbalances in the bio–psycho–social complex adversely affected integrated treatment planning. For example, it is widely held that deinstitutionalization was facilitated with the introduction of neuroleptic drugs. State hospitals were necessary before the advent of modern psychoactive drugs in the latter half of the twentieth century in order to grant asylum to the mentally ill (Lamb, 1988). By implication, state hospitals were no longer necessary after the advent of psychoactive drugs, in particular, neuroleptics and tricyclic antidepressants. Mosher (1975) credits phenothiazines for the dramatic decline in the population of schizophrenic patients residing in state and county hospitals. Controlled studies reviewed by Uhlenhuth, Lipman, and Covi (1969) and by May (1968, 1971) showed that, in general, little difference was found between psychotherapy plus drugs and drug therapy alone for hospitalized schizophrenic patients. Emphasis in the immediately above studies was on neuroleptic medications as the mainstay of treatment of schizophrenic patients discharged into the community. In retrospect, it seems that from the vantage point of the clinician, lack of adequate psychosocial supports in the community impeded patient capacity for satisfactory community tenure and the so-called "revolving door" problem emerged. It is common practice today in state and veterans administration mental health systems for provision to be made for access to follow-up care and treatment via satellite clinics, patient sponsors, case managers, out-reach programs, and supportive housing. All of the foregoing have contributed to the improvement of successful maintenance of patients in the community. The current dominance of the biological model in psychiatric research and treatment, therefore, needs to expand to include more psychosocial dimensions.

2. Medical schools and academic institutions exert a strong influence in setting the standards of care and thus lead the pursuit to identify biological markers for psychiatric disorders. Even though biological markers are yet to be validated they may hold currency in the psychiatric encounter. Once a specific lab test, imaging study, or complex investigative procedure is performed, it tends to skew the expectation of the patient toward a biological cure with relegation of psychosocial approaches to a minor role. Patients to this day present themselves as suffering from a "chemical imbalance." Such

presentation of specificity, whether it be for psychosis, depression, or anxiety disorders signifies an expectation of a specific therapeutic intervention: namely, a corresponding psychotropic medication. In keeping with current orientation, the expectation will almost certainly be met with a focus on variation in psychopharmacological interventions. Psychotropic medications have come to dominate psychiatric treatment. They can reduce sensory aberrations and facilitate psychological awareness. Given the residual pathology of most patients, however, psychological factors will continue to play a significant role in patient management. Programs which neglect these can achieve only limited success.

3. Therapeutic options may be constrained if pathogenesis is viewed as a single entity. Specific therapeutic interventions and single etiology clinics may be effective if there exists an established etiology, as for example in phenyketonuria or in Wilson's Disease. Nearly all clinical situations, however, involve the dynamic complexities of human beings burdened with a psychiatric disorder whose clinical manifestations have multidetermined and interrelated derivatives from biological and psychosocial factors. This is to say that psychological events, perceptions, and images are an inherent part of every individual's central nervous system development and are mediated via biological activities.

Specific notions of psychological pathogenesis may constrain therapeutic options as well. Consider psychotherapy set around specific events in patients' illnesses, which determine the therapeutic pathway. Initially, for example, separate groups are commonly organized for the treatment of alcoholics, or for victims of abuse, which may be further differentiated according to physical, emotional, or sexual subtypes. Similarly, psychotropic medication therapy in hospital settings or in clinics is frequently specialized and structured according to presumed patient pathology such as may be found in affective or anxiety disorder clinics. The DSM–IV has set forth defined criteria from which a specific diagnosis is reached and the diagnosis, in turn, serves as a guide to treatment with specialized protocols. Specialty clinics, however, are not that easy to sustain because of the complex conditions of patients. There is a tendency, therefore, for the special clinics to become exclusionary and admission to them is gained only after a screening process with negotiations between the specialty unit and the referral source. Patient census in specialty clinics tends to run low because of selective admission criteria — in spite of being established as a result of a perceived need. Special protocols for treatment in such units usually entail preconceived psychoeducational material formally presented by staff with follow-up discussion of the clinic's tenets in group or individual sessions.

4. The discovery and elaboration of receptor specificity and corresponding neuroleptic drugs led to simplistic approaches to complex problems. The

belief that laboratory findings could readily translate into the real world of multifactorial expression of mental disorders gave rise to certain clinical treatment approaches, of which biopsychiatry is the prime example.

Once a specific neurophysiological pathogenesis is assumed, lack of response to the class of drugs is often managed by variations in dosage from low to high. "Rapid neuroleptization" and high dose regimes are two discarded treatment approaches which come to mind as examples that were (are) less than salutary for patients. The effort to target various dysfunctional metabolic or enzyme villains usually involves combinations of drugs leading to "across the board" acceptance of polypharmacy. It is well known that patients who are prescribed high doses or polypharmacy regimens experience increased risks in terms of extended side effect profiles and drug interactions.

Conclusion

The concept of a single etiology for a corresponding psychiatric disorder is invalid from both psychological and biological perspectives. Selections from the literature were presented to support this view. Specificity has been especially reinforced by studies seeking to identify biological markers. A study, however, must go beyond a suggestion to validate the etiology of a psychiatric disorder and its establishment with a specific biological marker in order to satisfy customary scientific standards. In spite of biological targeting of specific CNS receptors and enzymes, however, it should be borne in mind that psychiatric disorders are multi-determined and complex. Specificity of pathogenesis insinuates to specific interventions and treatment protocols. This type of sequence has appeal to third party payers who, unfortunately, negotiate for specific treatment service limitations. Accumulated biological data, however, have failed to provide a valid test for a single psychiatric disorder. Of course, psychological factors influence the lines of study undertaken to determine the etiology of mental illnesses. Those factors subsequently bear influence on clinical settings and treatments. Specific contributing factors leading to the outcome of a psychiatric illness are inherently processed by individual patient dynamics in the context of a patient's unique biological, psychological, social histories as well as present functioning. The conclusion arrived at here is that treatment settings and strategies in psychiatry should be derived from a balanced appreciation of interactive etiological diversity.

References

Arlow, J.A. (1981). Theories of pathogenesis. *Psychoanalytic Quarterly, 50*(4), 488–515.

Aylward, E.H., Harris, G.J., Hoehn–Saric, R., Barta, P.E., Machlin, S.R., and Pearlson, G.D. (1996). Normal caudate nucleus in obsessive–compulsive disorder assessed by quantitative neuroimaging. *Archives of General Psychiatry, 53*, 577–584.

Bateson, G., Jackson, D.D., Haley, J., and Weakland, J. (1956). Toward a theory of schizophrenia. *Behavioral Science, 1*, 251–264.

Brodie, J.D. (1996). Imaging for the clinical psychiatrist: Facts, fantasies, and other musings [editorial]. *American Journal of Psychiatry, 153*, 145–149.

Damasio, A.R. (2000). A neural basis for sociopathy [commentary]. *Archives of General Psychiatry, 57*, 128–129.

Fleming, J.A. (1994). REM sleep abnormalities and psychiatry. *Journal of Psychiatry and Neuroscience, 19*, 335–344.

Fried, P.A. (1972). Septum and behavior: A review. *Psychological Bulletin, 78*, 292–310.

Fromm–Reichmann, F. (1948). Notes on development of treatment of schizophrenics by psychoanalytic psychotherapy. *Psychiatry, 11*, 263–273.

Garey, R.E., Heath, R.G., and Harper, J.W. (1974). Focal electroencephalographic changes induced by anti-septal antibodies. *Biological Psychiatry, 8*, 75–88.

Gonzalez, M.B., Cousins, J.C., Doraiswamy, P., and Murali, D.P. (1996). Neurobiology of chronic fatigue syndrome. *Progress in Neuro–psychopharmacology and Biological Psychiatry, 20*, 749–759.

Gruzelier, J.H. (1999). Functional neuropsychophysiological asymmetry in schizophrenia: A review and re-orientation. *Schizophrenia Bulletin, 25*, 91–120.

Gur, R.E., and Chin, S. (1999). Laterality in functional brain imaging studies of schizophrenia. *Schizophrenia Bulletin, 25*, 141–156.

Heath, R.G., Guschwan, A.F., and Coffey, J.W. (1970). Relation of taraxein to schizophrenia. *Diseases of the Nervous System, 31*, 391–395.

Itil, T.M., Marasa, J., Saletu, B., Davis, S., and Mucciardi, A.N. (1975). Computerized EEG: Predictor of outcome in schizophrenia. *Journal of Nervous and Mental Disease, 160*, 188–203.

Koyama, T., and Yamashita, I. (1992). Biological markers of depression: WHO multi-center studies and future perspectives. *Progress in Neuro–psychopharmacology and Biological Psychiatry, 16*, 791–796.

Lamb, H.R. (1988). Community psychiatry and prevention. In J.A. Talbott, R.E. Hales, and S.C. Yudofsky (Eds.), *The American Psychiatric Press textbook of psychiatry* (pp. 1141–1160). Washington, D.C.: American Psychiatric Press.

Lewis, D.A. (2000). Editorial. *American Journal of Psychiatry, 157*, 1–2.

May, P.R.A. (1968). Anti psychotic drugs and other forms of therapy. In D.H. Efron, J.O. Cole, J. Levine, and J.R.W. Henburn (Eds.), *Psychopharmacology: A review of progress, 1957–1967* (pp. 1155–1176). Washington, D.C.: United States Government Printing Office.

May, P.R.A. (1971). Psychotherapy and ataraxic drugs. In A.E. Bergen and S.L. Garfield (Eds.), *Handbook of psychotherapy and behavior change* (pp. 495–540). New York: John Wiley and Sons.

Mazure, C.M., Quinlan, D.M., and Bowers, M.B. Jr. (1997). Recent life stressors and biological markers in newly admitted psychotic patients. *Biological Psychiatry, 41*, 865–870.

Mosher, L. (1975). Schizophrenia: Recent trends. In A.M. Freedman, H.I. Kaplan, and B.J. Sanduck (Eds.), *Comprehensive textbook of psychiatry* (Volume 1, pp. 982–991). Baltimore: Williams & Wilkins Company.

Petty, R.G. (1999). Structural assymetries of the human brain and their disturbance in schizophrenia. *Schizophrenia Bulletin, 25*, 121–139.

Raine, A., Lenez, T., Bihrle, S., Casse, L., and Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry, 57*, 119–127.

Ravindran, A.V., Bialik, R.J., and Lapierre, Y.D. (1994). Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine: I. Platelet monoamine oxidase and the dexamethasone suppression test. *Journal of Affective Disorders, 31*, 111–117.

Siegel, M., and Tefft, H. (1971). "Pink spot" and its components in normal and schizophrenic urine. *Journal of Nervous and Mental Disease, 152*, 412–426.

Smith, G.S., Dewey, S.L., Brodie, J.D., Logan, J., Vitkun, S.A., Simkowitz, P., Schloesser, R., Alexoff, D.A., Hurley, A., Cooper, T., and Volkow, N.D. (1997). Serotonergic modulation of dopamine measured with [11C] raclopride and PET in normal human subjects. *American Journal of Psychiatry, 154*, 490–496.

Stabenau, J.R., Creveling, C.R., and Daly, J. (1970). The "pink spot," 3,4-dimethoxyphenylethylamine, common tea, and schizophrenia. *American Journal of Psychiatry, 127*, 611–616.

Symonds, L.L., Olichney, J.M., Jernigan, T.L., Corey–Bloom, J., Healy, J.F., and Jeste, B.V. (1997). Lack of clinically significant gross structural abnormalities in MRIs of older patients with schizophrenia and related psychosis. *Journal of Neuropsychiatry and Clinical Neurosciences, 9*, 251–258.

Szymanski, S., Kane, J.M., and Lieberman, J.A. (1991). A selective review of biological markers in schizophrenia. *Schizophrenia Bulletin, 17*, 99–111.

Uhlenhuth, E.H., Lipman, R.S., and Covi, L. (1969). Combined pharmacotherapy and psychotherapy: Controlled studies. *Journal of Nervous and Mental Disease, 148*, 52–64.

Vogeley, K., Schneider–Axmann, T., Pfeiffer, U., Tepest, R., Bayer, T.A., Bogerts, B., Honer, W.G., and Falkai, P. (2000). Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. *American Journal of Psychiatry, 157*, 34–39.

Wolf, S.S., Hyde, T.M., and Weinberger, D.R. (1994). Malformations of the septum pellucidum: Two distinctive cases in association with schizophrenia. *Journal of Psychiatry and Neuroscience, 19*, 140–144.

Wright, C.W., Rabe–Hesketh, S., Woodruff, P.W.R., David, A.S., Murray, R.M., and Bullmore, E.T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry, 157*, 1–25.