

Pseudoscience in Biological Psychiatry

Exploring Science, Evidence, and Mental Health

Second Edition



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Research Open

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Introduction

Dr. Colin A. Ross

In 2025, John Wiley and Sons, publisher of the original 1995 edition of *Pseudoscience in Biological Psychiatry*, notified me that the book had gone out of print and copyright had reverted to me and Alvin Pam, co-authors and co-editors. I decided to republish the chapters by the two of us with an additional chapter reviewing papers published in *The American Journal of Psychiatry* in 2022-2025.

Fundamentally, nothing has changed in biological psychiatry in the last 30 years. There have been changes in content but the pervasive errors in logic and scholarship analyzed in 1995 still dominate and control the field. *Pseudoscience in Biological Psychiatry* is still an apt title.

In What Sense Is Biological Psychiatry A “Pseudoscience”?

Alvin Pam

Biological psychiatry is devoted to the investigation of constitutional determinants of psychological disorders, with a goal of devising corresponding preventive or remedial measures for whatever may be amiss in the human organism. This task is carried out using scientific method, which involves empirical research, statistical analysis, and formal inferential logic. In many respects, biological psychiatry has adhered to scientific standards - for example, the field of psychopharmacology has been rigorous in its testing of new drugs. Although it is true that even this applied field has its detractors - most recently, Breggin (1991) - such charges as misuse of medications and “toxic psychiatry” do not constitute an attack on the scientific foundation of psychopharmacology. Rather, debate about efficacy, side effects, and the role of drugs in psychiatric treatment is consonant with the spirit of scientific research, ultimately fostering the development of more effective new compounds with reduced toxicity profiles.

So where is the “pseudoscience”? The purpose of this book is to show that biological psychiatry - presently the dominant force within the discipline of psychiatry - is dominated by a reductionist ideology that distorts and misrepresents much of its research. This ideology goes far beyond a mere conceptual frame for the treatment of patients; it defines *somatic variables* as the prepotent factor in the etiology of “abnormal” behavior. According to its tenets, the individual with behavior problems must suffer in some way from defective protoplasm, a constitutional predisposition to mental illness. The psychiatric symptoms of patients thus warrant research into etiology and treatment along the same lines as the physical symptoms of patients in general medicine. Given this stilted, unidimensional, and mechanistic world view, research in psychiatry has been geared toward discovering which aberrant genetic or neurophysiological factors underlie and cause social deviance. In such investigations, the ideology implicitly structures the experimental methodology and the inferences drawn from the data. The resultant body of work forms a professional “literature,” which then becomes the basis not only for the training of apprentices in psychiatry, but also for the education of the public on psychiatric matters. It becomes part of the culture. At the same time, biological psychiatry is a product of its culture. Unless challenged, contemporary culture will progressively regard *homo sapiens* as *homo biologicus* - something on the order of a highly evolved, intricately wired, and socially verbose fruit fly.

The “model of man” propounded by biological psychiatry is a parochial medical approach to psychopathology, but it has vast implications for other disciplines, most notably the social sciences. In addition, it has significant public health, legal, and political ramifications. In the course of pursuing its goals, biological psychiatry claims for itself a scientific status based on empirical research, so that its findings are beyond criticism from any other discipline. Accordingly, these findings can only be criticized, according to biological psychiatry, from inside biological psychiatry - that is, through new information provided by fresh research, innovations in methodology, and reviews or reevaluation of old data. The nature of knowledge in the field has disturbing elements of ontological solipsism.

It follows from the above that a critique of biological psychiatry must start with an assessment of its scientific status. Is the methodology sound? Are the inferences valid? Is the “model of man” compelling? The present book begins with a chapter by Pam, who evaluates the field’s methodology and inferential logic. Pam concludes that this body of work has all the accoutrements of science but is grossly lacking in the most elementary aspects of experimental design and interpretation of data. He offers evidence that biological psychiatry does little to criticize its own premises and thus recapitulates the same errors over time.

Moreover, it wields a strong public-relations arm, which manipulates the press into heralding its “breakthroughs,” although very little of scientific merit is actually occurring. In its march toward scientific “progress,” biological psychiatry tends to endorse fads - if one may speak of research efforts in this way - that momentarily “explain” in sophisticated terms the physiological etiology and mechanics of various syndromes and diagnoses. Later, such results are not replicated, and specific hypotheses quietly fade away while the general theoretical approach remains.

Pam cannot focus on the current state of each area of biological research because his chapter would soon be outmoded by the flood of new papers. Instead, he points out unchecked errors in procedure and logic that can be found across many studies in different areas and represent pervasive “blind spots” in a prolific literature. The chapter is an expansion and updating of a monograph originally published in *Acta Psychiatrica Scandinavica* (1990) and is intended for an audience interested in psychiatry but not necessarily wanting a technical exposition of research design and findings. However, the chapter does serve as a rough primer in how to evaluate research.

Blaming The Body

Biological psychiatry has always had to perform social functions that are supportive of established authority, especially in times of marked social inequality or retrenchment. In its search for such biological defects as genetic anomalies, abnormal brain morphology, and neurotransmitter dysregulation as primary etiological factors, biological psychiatry tends to “blame the body” for disturbed behavior, rather than the family or society. This perspective lets the social surround escape unscathed from any blame or responsibility, no matter how much psychological disorder is in its midst. The inherent bias in a reductionistic biological psychiatry is that no one - not even the afflicted individual - is accountable for his or her behavior, because abnormal behavior is presumed to have some impelling pathophysiological cause. Human choice and values are negated, and the sociocultural status quo remains intact. Thus, an overly biologized psychiatry becomes an instrument with which to repress alternative psychosocial models of psychopathology.

Since Freud, symptoms have been understood as a nonverbal protest: a symptom conveys the bitter message that developmental needs have not been met, resulting in unmistakable signs of suffering, as well as a metaphorical acting-out. However, biological psychiatry does not accept the Freudian perspective that symptoms are a desperate, counter-productive, indirect communication. Rather, in response to a patient's symptoms, a biological psychiatrist typically offers a medication that will “correct” a putative biochemical imbalance. Given such a narrow base for clinical intervention, the prescribing of a psychotropic medication (which may be pragmatically quite helpful) may produce a destructive end result. This is because dispensing a pill can reinforce a pseudoscientific biological determinism that covers over or distorts the patient's actual social situation. In such cases, even good psychopharmacology can be bad medicine!

Biological factors enter into all behavior, including symptoms, but only rarely are the cause and significance of a patient's behavior primarily biologically driven. It is more accurate to view the body as *mediating* the expression of affect and purpose for the whole organism. Thus, contrary to the model of humans upheld by biological psychiatry, in which such agencies as genes, lesions, or neurotransmitters direct behavior, this book supports an alternative “trauma model” in which psychopathology is usually caused by external events precipitating a psychological crisis. The body activates and adjusts itself as it deals with the crisis, and it adapts itself quasi-permanently - as a result of the crisis - to a different experience of the environment. Treatment should inclusively address three factors in each case: (a) the noxious aspects of the environment, (b) the tendency to psychologically construe the environment as “noxious,” and (c) the restoration of normal as opposed to stress-related somatic functioning. Only the latter requires medication, and medication may not be necessary if the first two aspects are ameliorated.

In short, we argue for the biopsychosocial paradigm that is, ostensibly, universally accepted by mental health professionals. However, this book would not be necessary if adherence to the paradigm were truly universal. We believe that biological psychiatry has made a travesty of the biopsychosocial paradigm, either by largely omitting psychosocial factors in its clinical formulations or by downgrading them to mere incidental “triggers.”

The Plan Of The Book

The organizational schema of this book needs to be outlined at this point. As stated above, the point of inception is the critique by Pam, a clinical psychologist, of the methodology and inferences of current research in biological psychiatry. The purpose of his chapter is to raise serious concerns in the reader's mind about the validity of relatively unchallenged data and conclusions, and the bias implicit in much of biological psychiatry's research.

Chapters 2 and 3 are by Ross, a psychiatrist specializing in the treatment of dissociative disorders. Chapter 2 reviews cognitive errors that are part-and-parcel of the training of psychiatric residents; they are imbibed without much discussion of the validity of these “scientific” assertions. Ross analyzes current biological psychiatric lore about the etiology of mental illness and the workings of “human nature” - both reduced by biological psychiatry to simplistic biomedical paradigms. Chapter 3 reviews articles published from 1990 to 1993 in the prestigious *American Journal of Psychiatry*, illustrating the extent to which psychiatry is now under the sway of biological determinism. Ross analyzes many of the articles to show that the methodology, statistics, and inferences are sub-standard, or the findings trivial or inconclusive, although the papers reinforce the image of psychiatry as a biomedical science.

References

- Breggin, P. (1991). *Toxic psychiatry*. New York: St. Martin's Press.
- Cloninger, C. R. (1993). Editorial: Unraveling the casual pathway to major depression. *American Journal of Psychiatry*, 150, 1137-1138.
- Pam, A. (1990). A critique of the scientific status of biological psychiatry. *Acta Psychiatrica Scandinavica*, 82 (Suppl. 362), 1-35.

The Historical Background

Alvin Pam

In a century of outstanding scientific progress, different branches of medicine have developed diagnostic and therapeutic techniques that have made previously dreaded diseases far more treatable, and in some cases even eradicable. As of this moment, similarly impressive progress is being reported in many areas of investigation by biological psychiatry; for example, preliminary findings on genetic markers for depression and schizophrenia have been published, both panic and obsessive-compulsive reactions have been induced in the laboratory by chemical means, and neurotransmitter abnormalities are under scrutiny in alcoholism, suicide, and other psychiatric disorders. Indeed, one takes for granted that progress will go on until constitutional mechanisms have been specified for every syndrome so that, in the near future, remedial pharmacological or other interventions can be applied. An indispensable formulary is already available for the treatment of most conditions, and the new drug treatments have resulted in much less reliance on institutional management and qualitatively better lives for mental patients. It is understandable that biological psychiatry takes much pride in this recent record of accomplishment.

However, all may not be as roseate as might appear at first blush. I do not refer to the lack of exact knowledge as to just what genetic or bio-chemical defect is involved in psychiatric disorders because causes are complex and it will take considerable time to work out intricate psycho-physiological sequences. What I mean is much more fundamental: bio-logical psychiatry cannot fulfill its mission properly because in its current state it has more the accoutrement of a scientific discipline than the substance. To be sure, this statement will raise skeptical eyebrows. It will be the burden of this chapter to spell out the grounds for such a broad iconoclastic assertion. To wit, I will be charged to show:

- (a) that the methodology of biological psychiatry is sufficiently flawed as to call into doubt the preponderance of its accepted findings, and
- (b) that an approach to psychopathology largely based on biological determinism introduces an ideological slant that selectively shapes the research that is done. Both of these criticisms already inhere in Gerard's avuncular dictum to the field of psychiatry—"no twisted thought without a twisted molecule" (Abood, 1960) - or van Praag's variant: "strange people, strange substances" (1977). When an approach to psychopathology is based on reductionist thinking, it projects a worldview that proclaims, in effect, *biology is destiny*. Because research activity inevitably will be influenced by such an implicit bias, my contention is that a biology-based orientation to what is called "mental illness" has generated an experimental methodology expressly crafted to emphasize the crucial role of somatic variables, with resultant data circularly used to validate a reductionist theory.

To demonstrate this thesis, the present chapter must chiefly be concerned with a critique of the methodology. For purposes of organization, I have adopted Akiskal and Webb's (1978) fourfold classification of methods of research into the "psychobiological interface": (a) pedigree studies, (b) pharmacological response studies, (c) neuropsychological-neurophysiological findings, and (d) biochemical correlates of emotion. Despite unavoidable overlap, their division of the scope of the field is as serviceable as any. I will review, in turn, historically significant investigations in each of the four topical areas so as to detail distinct limitations of the research, some inherent in the methods themselves and others arising from faulty application that may have gone unscrutinized. The methods in themselves are valid if there are biological variables to measure, but use of the methods (producing a copious literature) hardly constitutes ipso facto proof that the sought-after biological variables exist! With this warning in mind, it will quickly become apparent, as one reads along, that past and present research in all four areas has frequently led to dubious conclusions asserting the existence of requisite, usually prepotent biological factors.

My review will not attempt to be comprehensive in its treatment of any particular syndrome, nor will there be a sustained effort to keep up with the current status of research into the various psychopathologies (such an ambitious undertaking on my part would soon be out of date anyway). Instead, my focus is on analysis of technical fallacies endemic across research studies, as well as spurious inductions drawn as a product of investigator bias, overgeneralization, and markedly lower research standards than Lewontin, Rose, and Kamin (1984) believe would be tolerated anywhere else in science.

As analysis of representative work within the four areas will show, failure to meet standards of scientific quality can be mainly attributed to the misconceptions, prejudices, and tunnel vision that biological psychiatrists have brought into their research in the form

of unexamined and sometimes untenable *ideological* premises (Ingleby, 1980, 1981). Because virtually every psychiatric disorder is largely imputed to constitutional dysfunction, the problem is presumed to be “inside” the body of the patient rather than the product of an “outside” interaction. In this medical-model view, the immediate surround becomes in essence no more than a fortuitous “trigger” for a decompensation that was always latent within the patient’s physical being. Such an approach can be characterized as a “blame-the-victim’s-body” philosophy. Personal problems become tantamount to biological problems; indeed, the appropriateness and morality of action are soon converted via “the medicalization of social deviance” (Conrad, 1980) into a matter of laboratory values within normal limits. The question is never asked as to whether the body can indeed *cause* rather than merely *mediate* a psychiatric symptom-as if the body, which actualizes what we do, also tells us how to live (Lipowski, 1989). Ross (1986) has chided many of his colleagues for intrinsic reductionism: the *idee fixe* within the psychiatric field that a physical abnormality causes at least a predisposition in nearly all forms of psychic disorder, culminating in a search for the defining biological marker:

Dealing with symptoms or syndromes as if they were specific diseases reflects a trend in psychiatry to regard mental illnesses as biological entities, definable by laboratory tests, treatable in accordance with these tests, and monitored in the course of treatment primarily by calibration of test results. But in this surrealistic world of pseudo-entities, the psychiatrist abdicates reality to embrace biological reductionism. (p. 431)

The chapter concludes by summarizing both methodological and ideological errors typically encountered in research which, taken collectively, grievously compromise the scientific standing of biological psychiatry. Recommendations are then made; they are intended to im-prove the contribution of biological psychiatry to the mental health field by dint of establishing more stringent criteria for research design, interpretation of data, and theory construction.

Pedigree Studies

The aim of pedigree studies is to determine whether the onset of a given diagnostic condition is associated with some form of genetic diathesis. Examples of fruitful investigation have been the discoveries of the exact mode of chromosomal transmission of Huntington’s chorea, phenylketonuria, and other rare and well-defined neurological diseases. Biological psychiatry has always striven to find similar genetic transmission for the so-called “functional” disorders, and almost every psychiatric category has been the target of pedigree studies, with positive findings reported and generally accepted by the field for most of the major diagnostic groupings. Pedigree studies can be classified into three classic subtypes: (a) consanguinity research, (b) co-twin control cases, and (c) adoption comparisons. Each will be discussed in order, and then the latest addition to the subtype methodology - the genetic marker design - will be addressed. For ready reference, this section on pedigree studies will be schematically presented as outlined in Table 1.1.

Table 1.1. Paradigms and Respective Power of Pedigree Methodology

Method	Design	Power
Consanguinity, research	A. Psychiatric genealogy	Inconclusive
	B. Concordance rates	Inconclusive
	D. Concordance rates for MZ twins reared apart	Powerful but impractical
Adoption comparisons	E. Collaterals: comparison of rates for biological vs. adoptive relatives, especially parents	Suggestive
	F. Descendants: comparison of rates for children of index parents vs. children of controls	Suggestive
	G. Cross-fostering: rates of children of index parents and control adoptive parents vs. children of control biological parents and index adoptive parents	Powerful
Genetic	H. Identification: correlating a genetic marker with presence of the diagnosis	Powerful marker studies
	I. Prospective-longitudinal: predicting which members of a family unit will develop the disorder in adulthood	Conclusive

Consanguinity Research

Family inheritance is investigated in two ways: by tracing the psychiatric genealogy of an indexed subject, the “propositus,” who has the disorder (design A), and by noting the correspondence of a given diagnosis with degree of kinship (design B). The earliest

investigations of this type were carried out by American adherents of the eugenics movement started in Great Britain by Sir Francis Galton. Influenced by social Darwinism, these pioneer researchers declared they aimed to “purify the race” by identifying those individuals who were biologically unfit to be parents, with the purpose of weeding them out of the nation’s reproductive pool. But first they had to show that specific forms of human “degeneracy” (as they called most of the mental disorders) were indeed inherited conditions. The maiden study, *The Jukes* (1887), was by a prison superintendent, Richard Dugdale. His data showed extremely high rates of criminality and social parasitism through many generations traced in the Jukes’ genealogy, and he concluded that inherited and therefore untreatable antisocial tendencies made such families severe social liabilities. The Jukes study was generally accepted by the academic community for about 50 years, but was ultimately considered embarrassing and unworthy of scientific attention because it did not control for the effects of poverty and parental modeling. The mere fact that some form of psychopathology “runs in families” does not necessarily support a genetic etiology, because the psychopathology could be explained on the basis of environment alone. What remains pertinent about the Jukes study even today is that a genealogical methodology does not—either explicitly or implicitly—demonstrate there has been genetic transmission, in particular when family, cultural, and economic factors conduce to the psychopathology.

The next major report by a eugenics-oriented researcher was by Henry Goddard, a psychologist at Vineland State School in New Jersey, published as *The Kallikak Family* (1912). The propositus, Deborah Kallikak, was brought for admission at age 8 because her mother’s new husband would not accept an illegitimate child. Deborah was diagnosed “mentally deficient” and was taken off her mother’s hands for what proved to be a lifelong stay at Vineland. Goddard attributed the patient’s condition to inherited tendencies going back to the American Revolution when a young soldier-ancestor had an affair with a “feeble-minded” barmaid, resulting in a line of mental retardates originating from the child of this brief union (“Old Horror,” as he was later called); after a respectable marriage, another line descended from the same soldier resulted in an eminent New Jersey family. The two branches did not know they had a common progenitor. Goddard concluded from this pedigree study that mentally retarded persons should not be allowed to reproduce—and this reading of his data meant in practice that the staff at Vineland was instructed to do their utmost to prevent the rather beautiful Deborah Kallikak from having any opportunity for a sexual experience, marriage, or discharge from the institution (Smith, 1985). In 1927, the U.S. Supreme Court went further and approved new laws for sterilization because science had now shown that mental deficiency was inherited! The eugenics movement applauded Justice Holmes’s brief in *Buck v. Bell*, which declared: “Three generations of idiots is enough”; selective sterilization was seen as a necessary first step to ward civilized control of reproduction (Kevles, 1985). As might be expected, forced sterilization in the United States over the three decades it was legal was very disproportionately directed at single-parent African American women on welfare in the South (Chase, 1977). Extremely admired and influential for many years following its publication, the Kallikak book is nowadays rarely cited, for it has become a prototype of how *not* to trace psychiatric inheritance. Goddard’s tracking of ancestry involved reaching a diagnosis on scanty information, mostly hearsay gossip from aged relatives or neighbors, with classification reached by an untrained investigator told only to look for any signs of “mental deficiency.” This procedure violated the research canon of “blind” diagnosis. Worse yet, Goddard misled critics by falsely alleging that he knew the name and biography of the barmaid (Smith, 1985) and by retouching the photographs of the “bad” Kallikak branch to make them look sinister (Gould, 1981)! Beyond methodology, his genetics are remarkably confused, as described by Scheinfeld (1939):

Granted “Old Horror” was a degenerate because of bad heredity (and there is yet no evidence that “degeneracy” is inherited), by what gene mechanism did he become that way? No single dominant gene could produce any such complex condition, nor is there any known gene that can singly produce even feeble-mindedness. Recessive genes would have had to be involved. Which means that as such genes must come from both parents for the effect to assert itself [within one generation], no matter how chock-full of “black” genes the feeble-minded mother was, the worthy [father] had to be carrying such genes if the condition of his presumptive son, “Old Horror,” was due to heredity. And that would mean, in turn, that the “good” Kallikaks also received some of those “black” genes! (pp. 361-363)

Yet, no subsequent descendant of the “good” Kallikaks ever displayed “feeble-mindedness,” although they numbered in the hundreds by the time Goddard did his survey. Moreover, many members of the “bad” Kallikaks were found to be unlikely cases of retardation (indicating investigator bias) by Smith when he retraced and added to the family history 73 years after the appearance of Goddard’s book. The final irony is that Deborah herself was not retarded: she could read well, write creatively, read music and play the cornet, embroider dresses, do excellent carpentry and wood carving, sew well enough to make shirts, and wait tables (Chase, 1977)! She had a mental-age score of 9 years when tested by Goddard in 1911, but Chase has noted, “As with so many other second-rank psychologists then and since, Goddard was never to learn how to differentiate between a living person and that person’s IQ test score” (p. 146).

Currently, only certain forms of mental retardation are regarded as due to chromosomal abnormalities. Whereas serious retardation is now attributed to either inborn or incurred neurological deficit, mild cases-the vast majority-are seen as usually stemming from psychosocial deprivation or a mixture of deprivation and minimal brain damage (Scott & Carran, 1987). However, in the earlier years of the century, a eugenic conception of “intelligence” had a profound impact on American thinking about mental retardation, with far-reaching social and political consequences (Gould, 1981). Congress even apportioned its 1924 immigration quotas on Goddard’s “inherited mental deficiency” research, which was based on giving IQ tests to mostly non-English-speaking arrivals from various nations. Goddard had found Italians, Jews, Poles, and Greeks much less endowed with “innate potential” than longer-established immigrants from the British Isles, Germany, or Scandinavia. Prospective citizens from Asia, Africa, and Latin America were considered to dilute the quality of the national stock to a degree inimical to civilized standards. Educational and cultural parameters were not considered in obtaining these results. However, Goddard did state that low-IQ citizens could serve a useful purpose in doing the menial labor! Ultimately, his research was discounted as hopelessly classist and racist. At best, Goddard had shown that mental retardation, like criminality, tends to “run in families,” but once again a genetic interpretation of the data did not hold up to critical scientific scrutiny. This brings us to the beginnings of the modern era in psychiatric pedigree research, that is, to work that followed the lead of Dugdale and Goddard but was on a more sophisticated plane in terms of experimental technique and statistics so as to still be cited in contemporary textbooks and review articles. In the area of schizophrenia research, Franz Kallmann (1938, 1946) took up the eugenics cause, contending from the family genealogies he investigated that schizophrenia was in-bred and thus constituted a reproductive threat to society. He too did hearsay diagnosis of distant or dead relatives, while relying on hospital psychiatrists to diagnose the close relatives of patients they were treating (hardly a “blind” procedure). He did several concordance studies, arriving at figures higher than any subsequent researcher-for in-stance, his 68% concordance rate for the child of two schizophrenic parents compares with a risk of 34-44% in four other studies, according to Lewontin et al. (1984). Kallmann’s studies contain, at most, perfunctory reports on methods, and only seldom does he provide the case histories that might permit readers to form their own ideas about social context, clinical course, or diagnosis. He does not deal with the genetically im-possible fact of a schizophrenic who has no family history through many generations on either side (unless schizophrenia is a mutation), occurring in 36% of his own sample of 589 twins where sufficient information was available and later estimated to occur in up to 60% of cases of schizophrenia (Smythies, Coppen, & Kreitman, 1968). No explanation is offered as to why schizophrenia does not weed itself out of the human population by virtue of having no evolutionary value for survival, while reproduction rates are known to be low (Rosenthal, 1971). Like his predecessors who upheld eugenics, Kallmann never considered early environmental factors in accounting for how psychopathology is passed from one generation to the next.

In contrast to the homage Kallmann continues to receive as the first biological psychiatrist to research schizophrenia in many extensive, systematic, and technically advanced pedigree studies, his contribution has been called “bloodcurdling pseudoscience” by Lewontin et al. (1984). Kallmann’s mentor, Ernst Rudin, developed psychiatric genetics as a new form of science at the University of Munich and later served the Nazis when they came to power-indeed, Rudin helped draw up the 1933 Ger-man sterilization law for mental patients, as a member of a committee chaired by Heinrich Himmler.

Kallmann imbibed the hereditary “taint” hypothesis propounded by Rudin to explain all types of mental disorder, but his own career in Germany was blocked because he was Jewish. He was forced to interrupt his investigation of schizophrenia as an inherited disease until after emigration to the United States in 1936. According to his widow, Kallmann somewhat modified his research conclusions for humanitarian reasons: he attributed schizophrenia to a “recessive” gene to evade mass sterilization. But Lewontin et al. (1984) showed that Kallmann never compromised the rigors of science for any humanitarian aim. In an early paper, he argued for sterilization of schizophrenics *and* their apparently healthy siblings-just because schizophrenia was “recessive.” Two Nazi geneticists had to oppose him to protect the large pro-portion of the German people involved! Perhaps in reaction to the Nazis, who escalated from the forced sterilization of 225,000 mental patients to “euthanasia,” killing 400,000 mental patients in 1939-1940, Kallmann gave up his advocacy of sterilization and wanted the State to regulate the marriages of schizophrenics and their children and to use institutionalization in the last resort to enforce birth control (as Goddard had mandated for Deborah Kallikak). His attitude toward schizophrenics, and his notion of their “treatment,” was quite frankly proclaimed (Kallmann, 1938):

Since there is thus far no accurate means at our disposal for preventing the incidence of the schizophrenic psychosis in a tainted individual, it seems to be even more expedient and more urgent to carry out restrictive measures against the inheritance of the taint. In this way psychiatry would accomplish its part in making the biological quality of future generations an important matter for medical ... activity, by decreasing not only the number of schizophrenic patients, but also the number of heterozygotic taint-carriers, such as schizoid eccentrics, criminal adventurers, or other members of the lunatic fringe. (p. 3)

Note the ascription of political or social deviance to the schizophrenic “taint.” Kallmann simplistically blamed “bad” genes for much of what he thought degenerate in an otherwise estimable society (over-looking any input that society itself may have had in bringing on “degeneracy”). Contemporary genetic research into psychiatric disorder

has considerably cleaned up its act since the days of Kallmann, in an effort to redeem itself from the stigma of past associations. Modern eugenicists, such as Gottesman and Erlenmeyer-Kimling (1971), lament that hardly anyone these days continues to mind the quality of the hu-man gene pool because the old eugenics ideology attracted bigots and zealots eager to save future generations from a flood of so-called hereditary defects or taints, leading to “such humanity-shattering excesses (in the name of eugenics) as genocide in Nazi Germany, compulsory sterilization laws, and an immigration quota system [in the United States] based on national origin” (p. S1). Given the mortification of the scientific community after World War II as to this historical ramifications of psychiatric genetics, Kallmann’s connections to the eugenics movement in general and to Rudin in particular have had to be studiously ignored if his work is still to be respectfully quoted in nearly every review on the inheritance of schizophrenia. And so it is! In other words, Kallmann’s family concordance rates are removed from their eugenics context and then treated as bona fide, though outdated scientific data. For example, Liston and Jarvik (1976) are typical of the many authors who laud Kallmann’s contribution to psychiatric genet-ics; moreover, in the course of their appreciation of Kallmann as a scientist, they also go the atypical route of openly granting similar recognition to Rudin:

Rudin and Kallmann were pioneers on the frontiers of medical genetics. The trails they blazed were necessarily crude, and their early hypotheses and conclusions may seem rough-hewn today. While these two scientists, their contemporaries, and their successors may not have proved “conclusively” and to everyone’s satisfaction that schizophrenia is an inherited disease, they have come close; and the paths they cleared are now leading to new and continuing research challenges in the genetics of schizophrenia. (p. 92)

I take strong exception to this sort of tribute to Kallmann *qua* scientist, for there have been reasons all along to discredit Kallmann’s work, apart from his eugenics ideology. On grounds of lack of a methodology section alone, his results are automatically suspect-his reports should not have been accepted for publication, and no reputable researcher should cite his statistics without caveat. Indeed, the problem of statis-tics without accompanying procedures and data was recently brought home to the scientific community by the Cyril Burt scandal (Burt sup-plied data on the inheritance of intelligence in bogus twin studies) so that the finding that intelligence is mainly inherited has had to be re-viewed (Kamin, 1974). Getting back to Kallmann, his studies were not “blind” and he seemed to have had diagnostic suspicions about the relatives of schizophrenics that constituted a stereotype on the same order as Goddard’s. Moreover, the figures Kallmann presented are routinely inflated: he used an abridged Weinberg method for age correction, setting the age group at risk for schizophrenia as being 15 to 44, so that non-schizophrenic relatives still in that age group could be tabulated into the totals as half-schizophrenics, because they had not yet had adequate time to demonstrate that some 50% of them were indeed whole schizophrenics (Neale & Oltmanns, 1880)! When the usual Weinberg formula is applied based on a risk period of ages 15 to 40, the reported rates fall drastically (for example, the famous .86 concordance for MZ twins drops to .69). Further, it should be realized that the usual Weinberg calculation is already an overcorrection because the risk period for onset of schizophrenia is by and large between ages 15 and 25. Kallmann’s interpretation of data is as problematic as his methodology. He maintained he had demonstrated that concordance rates for relatives of schizophrenics were significantly higher than the almost 1% rate (.0085) expected in the general population, increasing to its highest level in first-degree relatives. In other words, genetic theory correctly predicted that siblings, parents, and children (first-degree relatives) would have higher rates than grandparents, uncles, aunts, nieces, nephews, and half-siblings (second-degree relatives) whose rate, in turn, would be higher than the 1% general rate. However, shortcomings in this approach can be seen in Slater’s (1968) summary of many studies, including Kallmann’s (see Table 1.2).

Table 1.2. Expectations of Schizophrenia for Relatives of Schizophrenics

Relationships	N	Schizophrenic	Expectation (%)
Parents	6,331	243	3.8
Siblings	7,571	659	8.7
Children	1,149	138	12.0
Uncles, aunts	3,376	68	2.0
Half-siblings	311	10	3.2
Nephews, nieces	2,315	52	2.2
Grandchildren	713	20	2.8
Cousins	2,438	71	2.9

Data from E. Slater, "A Review of Earlier Evidence on Genetic Factors in Schizophrenia," in *The Transmission of Schizophrenia*, edited by D. Rosenthal and S. Kety, 1968, Oxford, England: Pergamon Press.

Many inconsistencies in genetic predictions are contained in Table 1.2. Rates for children of schizophrenics are strikingly higher than for siblings, who in turn have markedly higher rates than parents. All of these collaterals are first-degree relatives. Further, parents' rates, between 3 and 4%, are barely higher than the 2 to 3% expectation for second-degree relatives, and the rates for the latter are themselves only slightly above the baseline 1% in the general population. Only with a very large N based on combined samples can statistical significance be reached that contradicts quite small differences among baseline, second-degree relatives, and parents. Further, the magnitude of Mendelian ratios is not at all approximated. Given a dominant model of heredity, expectancy rates are about 50% for first-degree relatives and about 25% for second-degree relatives. Given a recessive model, expectancy rates for first-degree relatives are about 25%; siblings are some-what more vulnerable to the disorder than either parents or children, and the latter two groups should be about equally vulnerable. However, children's rates are more than three times higher than parents' rates, which means that growing up with a schizophrenic parent puts one at far greater risk for schizophrenia than being the parent of a schizophrenic child—a fact that argues for nurture rather than nature because parents control the home environment. If there is assortative mating (meaning a schizophrenic has an above-average chance of marrying another schizophrenic), as is almost certainly the case, distribution of a recessive gene in the mate can no longer be presumed random and expectancy rates will correspondingly rise; thus, when both parents are known to be schizophrenics, the expected rate reaches 100%. None of the figures in Slater's above-cited list are anywhere near the magnitudes predicted by Mendelian theory. For example, Slater's data showed only a 36% incidence for the offspring of two schizophrenics. Explanations within biological psychiatry for the shortfall in expected magnitudes are of two kinds: (a) that environment plays some part in the pathogenesis—but this glibly slips in the presumption that genetic factors already account for the rest; and (b) that "incomplete penetrance" complicates the genetic effect, without any basis for this assertion other than conjecture and the plotting of graphs for hypothetical distributions. Even a convinced hereditarian like Rosenthal had to admit that explanation (b) was problematic: "Although the concept of [reduced penetrance] could and perhaps should be useful... many geneticists feel that it is too often used to make ignorance respectable, and that in human genetics, it has been abused to the extent that it is in danger of falling into disrepute" (1970, p. 29). Dumont (1984) added that incomplete penetrance is an "apologetic compromise" to hold onto a genetic approach that is unsupported either by data or by the science of genetics ("... to assume the structure [of a gene] can 'cause' the structure [of behavior] is an error of such magnitude as to be something like a thought disorder itself" (p. 332)).

The most serious breach in inductive logic committed by Kallmann was his use of kinship concordance rates to demonstrate genetic transmission of psychopathology. We have already noted that no family inheritance study can control for environment in human research; such data, therefore, are nowhere near "suggestive"—they are at best inconclusive and at worst misleading (as in the Jukes and Kallikak studies). This inferential limitation holds with respect to any consanguinity finding, even if the design and technique employed in the investigation were scientifically impeccable. Because environmental theories also predict that specific disorders will "run in families," genetic researchers can mention family genealogy and concordance rates to show that transmission by heredity is not excluded as a possible cause, but they must still bring to bear evidence from more powerful methodologies in order to prove a psychiatric condition is inbred. As will be seen, this is far from the case with consanguinity research even today.

Co-Twin Control Studies

The next line of evidence in pedigree studies is comparative rates for a psychiatric disorder in MZ twins vs. same-sex DZ twins (design C), but especially comparing diagnoses of MZ twins reared apart (design D). Kallmann (1946) did an extensive and much quoted study in the area of schizophrenia, giving the aforementioned concordance rate of 86% for MZ twins whether raised together or apart. Nevertheless, closer inspection throws serious doubt on the validity of this figure, not counting the Weinberg inflation. Kallmann defined "identical twins reared apart" by the criterion of at least five years' separation prior to the on-set of schizophrenia in one of them! Because his sample averaged 22 years of age at onset, with 12 years' average separation, it can be surmised that "reared apart" meant separation at an average of 10. In fact, even separation as late as this made a difference in Kallmann's concordance rates: 92% for MZ twins still living together but 78% for "reared apart" MZ twins. In any event, Kallmann's statistics are now regarded as "preposterous" in the opinion of Lewontin et al. (1984), who showed that the four most recent studies average out of 26% for MZ twins reared together.

Moreover, it is a misinterpretation of the higher concordance of MZ twins as compared to same-sex DZ twins to infer that hereditary factors are responsible. When cases are examined, it often appears that the schizophrenia is a *Jolie a deux*, or some variation of a shared

paranoia where each twin plays a central part in the other's delusional system (Jackson, 1960). Two recent books on twin symbiosis, by Wallace (1986) on elective mutism and Sacks (1985) on idiot-savants, describe ineffable communicative bonds between MZ twins for which there is no analogue between DZ twins. In short, because twins-especially MZ twins-share their childhood environment, it is not legitimate to construe differential rates of concordance as proof of genetic etiology. Such interpretation of data becomes another version of the "runs in the family" fallacy.

Proponents of the hereditarian point of view are mindful of this re-striction in pedigree methodology but have made strenuous efforts to nullify it. An entire line of research has been devoted to what is called the "equal environments assumption" (Plomin, Defries, & McClearn, 1980, p. 295)-namely that shared family environment is comparable for MZ and same-sex DZ twins. Kendler, Neale, Kessler, Heath, & Eaves (1993) listed four lines of empirical evidence for the "equal environments assumption." Each is described here briefly.

It is acknowledged that psychological similarity in twins is influenced by the similarity of their treatment by the social surround, but this situation is seen as an epiphenomenon brought about by their degree of physical resemblance. For example, Zerbin-Rudin (1972)-the daughter of Ernst Rudin-attempted to refute any environmental explanation of greater concordance rates in MZ than in DZ twins for schizophrenia by the following reasoning:

The large difference between the concordance figures for MZ and DZ twins cannot be explained exclusively by the more similar environment of MZ twins. If MZ twins create a similar environment through their greater similarity, they do so because of the greater inherited similarity in their appearance and response modes. Thus, in a roundabout way, we still come back to the importance of heredity. (p. 48)

Kendler (1987), in a reprise of Zerbin-Rudin, again contended that the environmental similarity of MZ twins is the result and not the cause of their similarity. To support his position, Kendler cited one study in which physical resemblance of MZ pairs did not correlate with concordance for schizophrenia. But it is unclear just what this is sup-posed to prove: bonds between MZ twins are partly a product of physical resemblance inducing others to treat them as a unit, but they are also a product of intimate contact and common experience-even if the twins can be told apart on sight.

The second method used to support the "equal environments assumption" involves direct observation of twins in the family setting. The method readily acknowledges that the social surround tends to treat twins, especially look-alikes, as a "unit," but a crucial distinction is drawn between events where the family arranges such similarity for twins (the "imposed environment") and events where the family is responding to behavior initiated by the twins (the "elicited environment"). In this vein, Morris-Yates, Andrews, Howie, and Henderson (1990) studied 343 same-sex twin pairs, checking the similarity of their early environment against their scores in adulthood on neuroticism, anxiety, and depression scales. As these researchers expected, MZ twins were treated much more similarly than DZ twins-a finding that, if taken at face value, would invalidate the "equal environments assumption." But, in their view, such a reading of the data would be false: their sample showed no correlation between imposed similarity and subsequent intrapair psychopathology and only a few barely significant correlations between elicited similarity and later psychopathology. In short, the measures they used seemed to indicate that a similar early environment did little to presage concordance in psychopathology in adulthood. However, this result still did not quite rescue the "equal environments assumption" from their own contrary data. The researchers then further inferred that because similarity imposed by the environment had no effect on concordance rates but similar treatment elicited by the twins' behavior from the environment did have some effect, the latter was arguably "a consequence of their genetic identity" (p. 325). Thus, they concluded that the "equal environments assumption" is valid-the twins make the environment similar! This twist put on the data is based on the premise that one can easily discern which behavior is "imposed" or "elicited"-although any family therapist will insist that encounters between parents and children are interactional. Moreover, twin co-behavior that "elicits" similar treatment from significant others is not a self-evident product of common genetic factors as soon as the twins are two people with a shared history and many conjoint interests.

1. The third method involves the correlation of similarity of environment with later indexes of personality, intelligence, and psychopathology. Because MZ twins have been repeatedly found to have a more similar environment both in childhood and adulthood than DZ twins, this research has to be done separately for each group. According to Kendler (1987), the combined results of various studies are unclear: some found no correspondence while others did.
2. The fourth method involves a comparison of trait similarity as a function both of "real" zygosity, as assessed by investigators, and "perceived" zygosity, as reported by twins or their parents.

When families, the community, and the twins themselves expect MZ twins to be more similar than DZ twins, and if this expectation influences trait similarity, then falsely classified MZ and DZ twins become crucial tests of nature versus nurture. Plomin et al. (1980) reviewed re-search on “misclassified zygoty,” occurring in 40% of pairs in the major study they cited (Scarr & Carter-Saltzman, 1979), and noted that those who falsely thought they were MZ or DZ twins resembled their biological groups on intelligence and personality tests more than their sup-posed groups-a finding that runs counter to what environmental theory would have predicted. “We can conclude from this [that the environmental variable of] labeling twins as identical or fraternal has little effect on their behavioral similarity” (Plomin et al., p. 296). However, although the MZ twins who thought they were DZ were less alike than correctly classified MZ twins, they were also more alike than correctly classified DZ twins-an equivocal result. In contrast, the DZ twins who thought they were MZ were more dissimilar on personality tests than either correctly classified MZ or DZ twins-a perplexing result that throws into doubt any simple interpretation of these data. The conclusion by Plomin et al. - that labeling has little effect on similarity - seems to be an overgeneralization based on one more or less favorable study.

In a more recent study using this same approach, Kendler, Neale et al. (1993) found misclassified zygoty in 15% of female twin pairs and found no evidence for a significant influence of perceived zygoty on major depression, generalized anxiety disorder, phobia, bulimia, and alcoholism. Limitations of the study were: the small number of cases in each of the five diagnostic categories (only 15% of this sample were considered misclassified zygoty as compared to 40% in the Scarr and Carter-Saltzman research); possible errors in investigator-assigned zygoty because blood specimens were not always taken; and the inclusion of twins who did not know their zygoty in the same statistical category as twins who disagreed about their zygoty.

Whatever the merits of current “perceived zygoty” research, social labels of MZ or DZ twinship are only one source of twin homogeneity - as noted above, due weight must also be given to the extent of intimate contact and common experience as formative factors. In this vein, Carson and Sanislow (1993) showed that concordance rates for schizophrenia are consistently higher for DZ twins than for siblings in general, pointing to the relevance of proximity to each other and shared life events in determining vulnerability to schizophrenia (and presumably other psychiatric disorders).

To date, I know of no paper that has reviewed research on the “equal environments assumption” as a body. Instead, various reports cite various favorable studies, but unless the research as a whole is examined, the contradictions between even the favorable studies go unexamined. For example, Livesley, Jang, Jackson, and Vernon (1993) used the co-twin control method to ascertain the genetic contribution to personality disorders, claiming a heritability range from 0 to 64% for different subtypes. They mentioned the equal environments assumption as critical to their methodology (p. 1827) and were able to state that they found no significant differences between their samples’ MZ and DZ twins in terms of similarity of early environments! Although it is not said, this is the opposite of nearly all other studies. Ford (1993) argued that the physical resemblance of MZ twins calls forth similar treatment, but regarded this phenomenon as an environmental variable; Zerbini-Rudin (1972) considered it a genetic variable. Different studies using different measures, usually self-report scales, report different results for concordance rates for psychopathology. This entire research area is a muddle, but one only sees in the literature that the equal environments assumption is being supported in study after study. I contend that most of these studies are not solid and that there is sophistry in the way inferences are drawn from data. In short, if the equal environments assumption does not hold, as I believe it does not, it becomes impossible to disentangle joint environment from joint heredity, so that co-twin control studies are finally just as inconclusive as other sub-types of consanguinity research.

Nevertheless, if MZ twins are truly reared apart from birth, then it does become theoretically possible to do conclusive genetic investigation. Kallmann’s dishonest definition of “reared apart” can be somewhat forgiven because necessity breeds a contrived solution-the research is invaluable and there simply are not enough cases to be found. In one U.S. nationwide survey (Newman, Freeman, & Holzinger, 1937), a mere 19 cases of MZ twins separated in very early life were identified, and none was schizophrenic. When Jackson (1960) raised questions about the genetic etiology of schizophrenia, he was able to locate only two concordant cases of MZ twins reared apart in the entire world literature! Given the crucial theoretical importance of these two cases, Jackson provided clinical vignettes, and these can be checked against the original published reports.

One of them, written by Kallmann (1938) based on his work in Germany, concerned 22-year-old Kaete and Lisa, born to a psychotic un-married mother who could not take care of them. The twins were soon sent away, one to each of the mother’s brothers, both of whom were described by Kallmann as “eccentric borderline cases.” Kaete developed catatonic symptoms after the birth of an illegitimate child at age 15 and showed a deteriorative course in hospital except for a brief remission at age 16. Lisa showed “increasing helplessness and emotional indifference” and was placed at age 17 in the same Berlin hospital as her sister, also with a diagnosis of schizophrenia. This case is concordant for schizophrenia but has several drawbacks as a “genetic” study: the twins were separated from

a disturbed mother at an unspecified point in childhood, may have been reared in problematic foster homes, and had contact during their upbringing-scarcely conditions for a test of nature vs. nurture, especially when the subjects are in the care of their mother's siblings as the "environmental" aspect of the study!

The second case, reported by Craike and Slater (1945), actually called the concordant twin psychoses "*Jolie it deux*." Edith and Florence were separated at 9 months of age when their mother died, and did not meet again until age 24. Edith remained with her father and a new stepmother; at age 8, she was placed in a children's home for "anxious behavior" and stayed till 19! Her first paranoid symptoms occurred at age 20 while she was living with her father (who was described in the case study as a "brutal" man, without further details). She soon had to leave, eventually making her way as a domestic in London. When she encountered her twin sister there by chance, Edith accused Florence of "spying" on her and she held onto this idea ever after, but Edith was never hospitalized despite many peculiarities. Florence, however, was hospitalized at age 51, which is how the case came to the attention of Craike and Slater. Florence was sent to an aunt in London after her mother's death. She remained there, also working as a domestic, until her aunt's death in 1944, whereupon she promptly developed paranoid symptoms about her twin sister. This was the first time she had been symptomatic in her life, and the delusions quickly cleared in psychiatric treatment. Craike and Slater concluded that Edith was more disturbed than Florence and that both shared a schizophrenic disease. It can be objected that the history supports no such diagnosis for either twin, and they may have been contamination of independent diagnosis because the sisters were known to be MZ twins. Moreover, both twins were raised by relatives, and one had to deal with an apparently abusive father and spent 11 years of childhood in an institution.

Juel-Nielsen (1965) again searched the world literature on MZ-twins-reared-apart and found 2 more concordant and 3 discordant cases, for a box score of 4/7 concordant at that time. The third concordant pair came from Kallmann and Roth (1956): one twin developed schizophrenia in childhood and the other at age 18. Because no additional information was provided by these authors, we are without any case history material. The fourth pair, reported by Slater (1961), was greatly elaborated on and progressively brought up to date by Shields (1962) and Gottesman and Shields (1972, 1982). This case concerned Nicholas and Herbert, the illegitimate and soon-placed offspring of a Chinese-English adolescent about whom nothing seems to be known concerning psychiatric history. Nicholas was in three foster homes until age 4; Herbert was in two Roman Catholic nurseries until the same age. They met for the first time when they were evacuated from London during the Blitz. Upon their return to the city, their grandmother took custody, from ages 6 to 7. Nicholas was then sent to a stable foster home; Herbert remained with his grandmother, who was then remarried. At age 22, Herbert was hospitalized with an unusual clinical picture: Slater mentioned catatonic symptoms, delusional thinking, then "hysterical pseudodementia," which led to speculations about a "Ganser state or buffoonery syndrome." In the end, Slater reluctantly came to a diagnosis of schizophrenia. Upon learning that an MZ-twin-reared-apart existed, Slater immediately arranged for a psychiatric interview of this collateral and was no doubt amazed to hear that the twin had just been hospitalized himself with a diagnosis of schizophrenia! The background to these two first psychiatric admissions was as follows: on December 22, the two brothers had seen each other for the first time since age 7, and Nicholas learned that their mother had just visited England (she now resided in the United States) and spent time with Herbert. On January 5, Nicholas was admitted to hospital; on January 8, Herbert was admitted. Neither brother recovered and 20 years later they were still institutionalized. This case illustrates a more or less simultaneous schizophrenic break in identical twins who had very little contact up to age 22, and represents the best evidence from a co-twin control case for the genetic point of view. But their very unstable early history might account for the psychopathology of the brothers. There is also the common denominator of the grandmother (psychiatric history also unknown), who played a role in the upbringing of both boys. As for a precipitant, one can only wonder what the impact of their mother's surprise visit was on the child she saw, who then quickly communicated what had occurred to the child she had not seen.

In 1972, Gottesman and Shields reported more new cases and gave 7/11 as the concordance tally at that time; in 1982, these authors again surveyed the world literature and adjusted the count to 7/12 concordant cases. Their new material came from Inouye and Mitsuda in Japan, who discovered more MZ-twins-reared-apart in their country than the rest of the world combined! However, it was not a matter of Japanese willingness to separate MZ twins as was initially speculated; the large number of cases were mainly the result of overzealous reporting and shoddy selection. Of 15 pairs, only 1 had been separated at birth and only 4 before age 5; most were reunited after 2 years apart, and little or no history was offered to assess their environment or how they were diagnosed.

In summary of the co-twin control studies, it is doubtful whether one can argue that reared-together MZ vs. DZ twin comparisons can be imputed to a genetic differential: environment of MZ twins appears to be much more similar than that of DZ twins, even leading in some instances to an uncanny psychological symbiosis. Further, investigation of MZ-twins-reared-apart research has yielded far too few cases to draw conclusions: of only 12 known cases in the world in 1982, 5 were discordant; of the remaining 7, just the above-

described 3 were presented in sufficient depth to be scientifically useful. Moreover, in these 3 cases, we have seen that the children were raised over many years by uncle, aunt, father, or grandmother-a gross violation of the essential design of any nature-nurture experiment. Independent diagnosis has also been a concern in 2 cases reported in the literature.

The MZ-twins-reared-apart research is theoretically powerful, but in practice the method amounts to naturalistic observation. Because the rare cases “just happen,” they cannot be screened to assure an environment good enough to be conducive to the future mental health of each of the twins. Indeed, the cases are *by definition* confined to twins whose mothers could not or would not take care of them, with the twins separated from each other (but not necessarily at birth) and of-ten ending up in precarious foster situations or institutions. It there-fore follows that no reputable scientific paper should uncritically cite concordance rates for MZ-twins-reared-apart whenever essential case history data are lacking, or when such data are ignored in reaching a genetic interpretation.

Adoption Comparisons

As with MZ-twins-reared-apart research, adoption comparisons are theoretically capable of settling the nature-nurture debate; moreover, the problem of getting sufficient cases is readily solved by using a population pool of *all* children adopted at an early age (not just MZ twins), which allows latitude in sampling and the establishment of control groups. Hence, adoption comparisons today rightfully comprise the principal evidence for a genetic cause or for predisposition to a psychiatric disorder.

With regard to schizophrenia, the series of Danish papers by the American research team of Kety, Rosenthal, and Wender in conjunction with several Danish colleagues are of surpassing importance. However, some earlier studies are also reputable, most notably that of Heston (1966), where we shall start. Heston traced the history of 58 children born to schizophrenic mothers in Oregon state hospitals between 1915 and 1945. These children had been placed in foster care no more than 2 weeks after birth. Their 58 matched controls in the study were children who had been placed for adoption by the same agencies very soon after their birth, but whose mothers lived in the community and, as far as was known, were not schizophrenic. The results for the index and con-trol samples were reported in Table 1.3.

Table 1.3. Adopted Children to Schizophrenic and Nonschizophrenic Mothers

	Index Adoptees (N = 58)	Control Adoptees (N = 58)
Death in childhood	9	5
Lost to follow-up	2	3
	Index Group (N = 47)	Control Group (N = 50)
Schizophrenia	5	0*
Mental retardation	4	0
Sociopathic	9	2*
Neurosis	13	7

* Statistical significance at .05 level.

Modified from “Psychiatric Disorders in Foster Home Reared Children of Schizophrenic Mothers” by L. Heston, 1966, *British Journal of Psychiatry*, 112, pp. 820, 822.

Heston concluded that the finding of statistic significance for schizophrenia supported a genetic etiology. However, such significance may be an artifact of a flaw in research design: in Heston’s study, there is abundant evidence of *selective adoption* -the bane of all adoption studies. Prospective foster parents knew the background of each child, and the children of state-hospital mothers were much harder to place. Half the index cases and none of the control cases spent 2 years or more in institutions because of placement problems (Heston, Denney, & Pauly, 1966). In addition, Heston did not take into account that pregnant schizophrenics may not have received adequate prenatal care (Rosenthal, 1971), nor that schizophrenic mothers are prone to extraordinary rates of birth complications that can lead to neurologically im-paired neonates (Mednick, 1970). In connection with possible prenatal or perinatal damage, it can be pointed out that the childhood death rates were inordinately elevated in both groups, but were almost twice as high in the index subjects (9 / 58 = 16%). Finally, the data do not sup-port a purely schizophrenic interpretation but rather indicate, from a genetic point of view, that there is a nonspecific polypathological diathesis for those children who survived until adulthood (31 / 47 were schizophrenic, retarded, sociopathic, or neurotic, compared to 9 / 50 control cases). In short, Heston showed that schizophrenic women were likely to produce children exceptionally vulnerable either to early death or subsequent emotional disturbance. Further, it was not demonstrated that this

latter outcome was a product of genetic influence: comparatively poor adult adjustment could have been explained by a combination of neurological deficit and the difficulties of placing “bad seed” children.

This brings us to the studies conducted in Denmark, where the national health register permits researchers to check the diagnosis of virtually any adult in the population who came to psychiatric attention. Published largely between 1968 and 1974, the series can be conceptualized as consisting of three interlocking investigations:

1. Kety, Rosenthal, Wender, and Schulsinger (1968)-a study of *collaterals* (design E in Table 1.1); identified a sample of diagnosed schizophrenics who had been adopted in very early life, then proceeded to a comparison of rates of schizophrenia in their biological vs. adoptive relatives;
2. Rosenthal, Wender, Kety, Welner, and Schulsinger (1971)-a study of *descendants* (design F); identified a sample of adopted-away children of diagnosed schizophrenics, then proceeded to compare rates of schizophrenia in this cohort vs. those of adopted-away controls born of nonschizophrenic parents;
3. Wender, Rosenthal, Kety, Schulsinger, and Welner (1974)-a *cross-fostering* study (design G); compared rates of schizophrenia when adoptive but not biological parents had been diagnosed schizophrenic vs. rates when biological but not adoptive parents were so diagnosed.

It should be mentioned that a “schizophrenic” parent in any of the Danish series need not have been so at the time of the child’s birth, adoption, or even childhood-on average, the diagnosis was given 11 years after a child’s birth. No history was provided for any case. Let us now consider the results of the Danish series.

The Kety et al. (1968) study located 33 adoptees who were diagnosed schizophrenic as adults, and matched a control group of 33 other adoptees never so diagnosed. The average age of separation from the natural mother was 3.5 months for the former and 4.1 months for the latter, with age at transfer to an adoptive home 18.3 and 16.0 months respectively. The researchers traced 150 biological relatives (parents, siblings, and half-siblings) of the index cases and 156 control relatives. They found only 2 diagnoses of schizophrenia among all relatives, one in each group; in both groups, they found less than the 1% expected rate of schizophrenia in the general population! They then pooled together a larger nosological category-“schizophrenic spectrum disorder” - which included chronic and acute schizophrenia, borderline states, schizoid and inadequate personality, and uncertain schizophrenic or borderline conditions. With a bigger net, they caught more fish: 13 of the biological relatives of the index group (9%) were within the new “spectrum,” as compared to only 3 (2%) of the biological relatives of the control cases. This difference was statistically significant. The Rosenthal et al. (1971) study located adoptees given up by a parent who was at some time diagnosed schizophrenic, and matched a control group of other adoptees who had no known schizophrenic parent - a design quite similar to that of Heston’s investigation. However, whereas Heston’s subjects were separated from their natural mothers days after birth, the median age of separation was 5.9 and 5.8 months respectively for the two Danish groups. In their preliminary report (Rosenthal et al., 1968) the researchers found only 1 case of a schizophrenic adoptee from a schizophrenic parent; nevertheless, invoking the “spectrum,” they had a Danish colleague do “blind” interviews with the now grown-up children and had suggestive but not statistically significant results (13/39 index cases vs. 7/ 47 control cases). Shortly afterward, data from more cases were available and a final re-report was issued (Rosenthal et al., 1971); with an increased N, significance was now claimed (34/76 index cases vs. 12/67 control cases).

The Wender et al. (1974) study compared 69 children born to “schizophrenic spectrum” biological parents but raised by non-schizophrenic adoptive parents (the index group) with 28 children born to non-schizophrenic biological parents but raised by schizophrenic spectrum adoptive parents (the cross-fostered group); there were also 79 children from non-schizophrenic biological and adoptive parents (the control group). The median age of separation from the natural mother was 5.9 months for the index group, 4.5 months for the cross-fostered group, and 5.8 months for the control group (with a range for the latter from 5 days to a striking 7 years). Based on a new and apparently unvalidated “global psychopathology” interview-based scale (which for unstated reasons supplanted the previous history-based diagnosis of a schizophrenic spectrum disorder), no difference was found between the scores of the cross-fostered and control groups, just as would be predicted by genetic theory. More importantly, the mean score of the index group was significantly higher than that of the other two groups, *but only if* the latter groups were combined to make a large enough N. The combining of scores was done, and thus the reported results support the genetic hypothesis of the study. However, the price paid to obtain this outcome was costly: significance was achieved by sacrificing the cross-fostering design in the final statistical analysis, thereby rendering the findings equivocal.

Whatever their shortcomings, the Danish reports are without question the most comprehensive pedigree studies yet done. Snyder (1976) declared that they stand as a landmark contribution. Konner (1982) held the Danish adoption series to be “the best study so far in the whole field of human behavior genetics, and as close as human studies are likely to come to experimental rigor” (p. 97). Crowe (1982) hailed their collective findings as resolving the nature-nurture controversy so far as schizophrenia is concerned. Wender (1976) stated on behalf of the research team: “We failed to discover any environmental component” (p. 23). Wender and Klein (1981) extrapolated from the Danish adoption data that 8% of the general population are genetically predisposed to develop a personality disorder within the schizophrenic spectrum; only medication could correct the underlying biochemical problems. Rosenthal (1971) attributed 73% of the etiological variance for schizophrenia to genetic factors. Neale and Oltmanns (1980) stated: “If any doubt remained concerning the importance of genetic factors in schizophrenia, it was abolished by the [Danish] adoption studies” (p. 215). Strong claims from many quarters!

However, granted the deserved accolades for a prodigious investigation, the Danish adoption research is hardly beyond very serious reproach and does not singlehandedly settle the nature-nurture controversy. It cannot be contended that the series shows the heritability of schizophrenia; at best, two of the studies show the heritability of “schizophrenic spectrum disorder”-a vague and possibly non-homogenous condition. Even scholars as meticulous as Neale and Oltmanns elide this distinction, as can be noted in the statement quoted above. Moreover, biological psychiatrists often uphold and glorify the Danish studies by virtually disregarding the major criticisms that have found their way into the professional literature. Already, four devastating critiques have been published that should not be over-looked, especially in that the last three even impugn the scientific integrity of the Danish research team.

The first critique, by Benjamin (1976), noticed that none of the bio-logical parents of schizophrenic children in the Kety et al. (1968) study was schizophrenic, and that statistical significance came from 9 /13 schizophrenic spectrum biological relatives who were half-siblings by the father (see Table 1.4). In short, second-degree relatives had higher rates than first-degree relatives, and this result, Benjamin points out, is a violation of the principle that genetic effects increase with greater consanguinity. The study’s conclusion is therefore invalid on its face. In a second important critique of the Danish series, Lidz, Blatt, and Cook (1981) complained that in the Rosenthal et al. studies (1968, 1971) the researchers allowed cases of manic-depression to get mixed into the schizophrenic spectrum, and that these cases made the difference in achieving significant results because manic-depressive parents were just as fecund as schizophrenic parents in breeding offspring in the schizophrenic spectrum (see Table 1.5)! Because manic-depressive and schizophrenic genetic processes are held to be distinct, this study too can be considered invalid on its face. In addition, Lidz et al. called on the Danish team to publish the results of psychological testing they administered to all subjects so as to provide an independent means to reach blind diagnosis. The insinuation here was that the researchers were suppressing information presumably unfavorable to their genetic hypothesis.

Table 1.4. Diagnosed Mental Illness in the Biological Families of Index and Control Cases

Schizophrenic Spectrum Disorders in the Biological Family						
Proband Diagnosis	Parents	<u>Probands</u>		Parents	<u>Controls</u>	
		Sibs	1/2-sibs		Sibs	1/2-sibs
B1						
B2						
B3	B3		D1			
B3			B3			
B1		C				
B1	D3					
B1						
B1						
B1				B1	B3	
B2						
B3	C					
B1						
B3						
B2						

Bl								
Bl								
B2								
Bl		B3,B3,B3						
B2								
B3								
B3								
Bl		Bl						
B3								
B2								
Bl		D3						
B3*								
B3*								
B2					D3			
B3								
Bl								
Bl								
Bl								
Bl								
B3		B3,D3						
Totals	3+	1 +	9	= 13	2+	1 +	0	3

Proband biological relatives = 150

Control biological relatives = 156

Legend: Bl = chronic schizophrenia

B2 = acute schizophrenic reaction

B3 = borderline schizophrenic or schizoid C = inadequate personality

D1 = uncertain chronic schizophrenia

D2 = uncertain acute schizophrenic reaction

D3 = uncertain border line schizophrenic or schizoid

* Only one of a pair of MZ twins was counted as a proband.

Data from "The Types and Prevalence of Mental Illness in the Biological and Adoptive Families of Schizophrenics" by S. Kety, D. Rosenthal, P. Wender, and F. Schulsinger, in *The Transmission of Schizophrenia* (pp. 354-355), edited by D. Rosenthal and S. Kety, 1968, Oxford, England: Pergamon Press.

Table 1.5. A. Consensus Diagnosis of Sick Parents

Diagnosis	N
Bl	36
B2	7
B3	3
Bl/B3	2
Bl/B2	6
B2/B3	2
D	1
Bl/D	1
B/M	1
D/M	1
M?	1
M	8
Total	69*

Table 1.5. B. The Percent of Schizophrenia Spectrum Diagnoses in the Offspring, According to the Subcategory Diagnosis of the Parent

Parental Diagnosis	N # Examined	N # in Spectr	% % in Spectr
B1	24	7	29
B2	5	1	20
B3	2	1	50
B/	3	2	67
M or M?	5	2	40
Controls	47	7	15
Total/Average %	86	20	23

Legend: B1 = chronic schizophrenia

B2 = acute schizophrenic reaction

B3 = borderline schizophrenic

D = doubtful schizophrenia

M = manic-depressive psychosis

* [Note by A.P.:] Of the 69 parents, 8-11 were manic-depressive, or between 11 and 16% of the total.

Data from "Schizophrenics' Offspring Reared in Adoptive Homes," by D. Rosenthal,

P. Wender, S. Kety, F. Schulsinger, J. Welner, and L. Ostegaard, in *The Transmission of Schizophrenia* (pp. 382, 388), edited by D. Rosenthal and S. Kety, 1968, Oxford, England: Pergamon Press.

In a third critique, Cassou, Schiff, and Stewart (1980), a team of experts from the French National Institute of Medical Research, concluded that the Danish studies were inadequate and misleading; they even questioned the probity of the researchers for making claims to blind diagnosis that were belied, in their opinion, by the way cases were reassigned and statistics juggled. Cassou et al. also held that adoption studies are automatically invalid if case histories are not presented as to the circumstances in which a child is separated from its mother, as well as how the child subsequently fares in placement, so readers can judge whether that youngster was neglected, abused, or otherwise damaged before or after adoption, as well as whether the adoption was traumatic in itself. They refer to the probandi as "*enfants abandonnes*," subtly indicating by this choice of terminology the irony of using throwaway kids as proof that schizophrenia is genetically transmitted! Another issue surrounds *when* children are placed: few were taken at birth and thus many spent their first 6 months with their natural mothers - the "bonding phase" during which a disturbed woman might well have the most harmful impact on her progeny's development (Magid & McKelvey, 1987). There were even some children who spent well beyond 6 months with their natural mothers before being placed for adoption; in general, index cases were placed later and adopted earlier than control cases throughout the Danish series. One must wonder what the research criterion was for "early" separation, especially when we see that at least one child was included who was given up for adoption at nearly age 7.

The fourth critique was by Lewontin et al. (1984), who went so far as to insist that the data can be used to demonstrate that environment is decisive for schizophrenia, not genetics! They argue from the findings of the Danish studies themselves: virtually no schizophrenic parents produced schizophrenic children and virtually no schizophrenic children came from schizophrenic parents. Despite the negative impact adoption can have, Henig (1988) reported that 1 to 2% of Americans growing up in adoptive homes represent 10% of psychiatric inpatients-Kety's review of the Danish data (1983) makes it clear that the adopted-away offspring of schizophrenics fare much better in adult-hood compared to their home-raised brethren! The adopted-away off-spring had lower rates in adulthood than the baseline expectancy for schizophrenia in the general population (Lidz & Blatt, 1983)! Thus, the most important finding of the Danish studies may be an environmental effect: not being raised by one's schizophrenic parent turned out to be salutary in terms of ultimate mental health. Lewontin et al. also believed that the Danish researchers twisted their data to reach congenial conclusions-for example, by reporting pseudo-interviews with dead or absent relatives based on suppositions as to what they would have said (p. 224). In addition, Lewontin et al. offered evidence of glossing over the key issue of selective adoption: they show that 24% of adoptive homes for index cases had a foster parent who had been in a mental hospital vs. 0% for control cases (p. 223). The issue of selective adoption is further exacerbated by the fact that, in Denmark, foster care agencies deliberately place children in accord with social characteristics of their biological parents (Hutchings & Mednick, 1975), a factor that was un-addressed by the researchers.

But the Danish studies cannot so easily be paradoxically used to support environmental causality. Proponents of the genetic point of view maintain that the schizophrenic spectrum is not very different from Meehl's "schizotypy" or Heston's "schizoidia" and that the

heritability of the schizophrenic spectrum is borne out in several smaller replications of the Danish design (Heston, 1970) and the more recent Roscommon family study (Kendler et al., 1993a, 1993b). At this moment in time, we can only wonder whether the glass is half-full or half-empty. Despite the vehemence of such as Paul Meehl (1972), who asserted it was not interesting to talk to anyone who disputed the contention that schizophrenia was inherited, the genetic etiology of the disorder is still nothing more than a hypothesis. Just as Jackson said in 1960, one can merely repeat in 1994 that a hereditary predisposition to schizophrenia is not a proven scientific fact.

Genetic Marker Studies

A new methodology in family pedigree studies is represented by the search for anomalies on particular chromosomes that can be traced across generations (design H in Table 1.1). With modern technology, a molecular design can now be utilized, specifying the mechanism within the DNA by which hereditary transmission of psychiatric disorders takes place. Such an approach forms the basis of a paper by Egeland et al. (1987), linking manic-depressive disorder to a single gene on the short arm of chromosome 11; this work was done on subjects from the Amish community in Pennsylvania.

After making allowance for the natural enthusiasm greeting a promising new avenue for research, some of the same old problems in pedigree studies are already evident in the professional response to Egeland: her results were initially accepted as if genetic transmission were an *a priori* truth just waiting to be shown, with scientific criticism suspended just as has generally been the case with the Danish adoption series. Egeland's findings should have been seen as merely speculative-the "marker" she observed may or may not have to do with genetic transmission of depressive traits. Definitive confirmation depends on replication of the data across many investigations, as well as on *predictions* based on the putative genetic marker as to which family members would be vulnerable in the future (design I), to be ascertained by longitudinal research. Pending such data, scientific acceptance of her results must be held in abeyance. In contrast, from the very date of publication, there was already reason for skepticism: in the same issue of *Nature* in which Egeland reported her findings, a similar study done in Iceland (Hodgkinson et al., 1987) found no linkage to chromosome 11 but concluded that "... mutations at different loci are responsible for the manic-depressive phenotype in the Amish and in Iceland" (p. 805). Both papers brim with high-tech molecular biology, but taken together they stand in contradiction. Although Egeland pointed to family history as proof that depression is inherited, the idea of a "mutation" can make any family history superfluous. The proposition that different ethnic groups have their own distinct genetic channels to manic-depression utterly denies the biological unity of the human species and runs counter to the basic premise of anthropology, which accounts for differences between ethnic groups on cultural rather than constitutional grounds. It boggles the mind to see "mutation" given as a reason for different results across populations when common sense would simply take this to be a failure of one study to replicate another, throwing doubt on the findings of one or the other. Moreover, the technology that is supposed to finally identify the predisposing gene for manic-depression did not consistently implicate chromosome 11, nor did Egeland's research confirm the presence of anomalies on chromosomes that had been specified in other research. The "News and Views" editor of *Nature*, Robertson (1987), synthesized the findings, citing two more marker studies not supportive of Egeland's chromosome 11 but concluding that therefore several genes must be causally involved in manic-depression-in other words, everybody could be right! No one considered in this issue of *Nature* that perhaps the data indicated that medical genetics are not germane to the study of depressive disturbance, and may even be neo-Lamarckian by viewing symptoms possibly acquired in the course of noxious family circumstances as genetically transmissible.

Following Egeland's model, linkage studies for schizophrenia have now also appeared in print. Bassett, McGillivray, Jones, and Pantzar (1988) encountered an odd-looking first admission while on psychiatric duty in a Canadian hospital and learned the patient had an uncle similarly odd-looking and emotionally disturbed: both men had a flat head, widely spaced eyes, protuberant ears, short stature, obese body, fusion of fingers, shortened toe, left kidney abnormality, small phallus, and-intriguingly-onset of schizophrenia at age 20. The rest of their immediate family was free of physical or mental deviance. On cytogenetic study, anomalies were noted in the Sq segment of chromosome 5 in the two men, but not in the rest of the family, except for their mother-sister who was a "balanced translocation carrier." Based on her "one-in-a-million" chance discovery, Bassett suspected that she had stumbled across the genetic mechanism predisposing to schizophrenia! However, she did not provide any case histories of the two probandi, nor did she conjecture whether their physical peculiarities in some neurological or psychological way contributed to the onset of schizophrenia. Even the question as to how they could possibly be prototypes for the schizophrenic condition did not arise-after all, very few schizophrenics look this way! She simply took for granted that a partial trisomy chromosome 5 resulted in deformity *and* schizophrenia.

This cause-effect logic can be criticized as nothing but the circumstantial evidence of a correlation in a single family pedigree.

Bassett's encounter with her unusual patient soon led to a funding grant for the next research step: an investigation of 7 families in

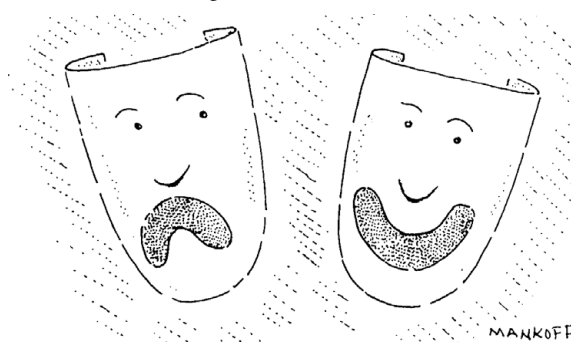
Iceland and Britain, with 2 families showing evidence of chromosome 5 abnormality in their schizophrenic members (Sherrington et al., 1988). However, another study co-reported in the same issue of *Nature* (Kennedy et al., 1988) did not find evidence for chromosome 5 abnormality in schizophrenic Swedish families, but once more speculated that mutations could account for differences between ethnic groups. The “News and Views” editor, this time Lander (1988), again posited that different genes could independently cause schizophrenia, so that all the marker studies might be valid despite the obvious problem of non-replication. The incongruent findings were presented as if important progress had been made in the genetics of schizophrenia. Noting these scientific developments, on November 10, 1988, the front page of *The New York Times* announced that the chromosomal aberrations leading to schizophrenia may have been discovered!

The next year, these early genetic marker studies had to be retracted for both manic-depression and schizophrenia (Schmeck, 1989). The indisputable failure to replicate was the main problem. In addition, prospective-longitudinal data showed that 2 subjects from Egeland’s Amish pedigree *without* the chromosomal abnormality developed manic-depressive disorder. From a research point of view, Egeland had properly applied scientific standards and accordingly withdrew her hypothesis. However, because of this failure, eminent biological psychiatrists are now convinced that multiple sites must be involved in manic-depression and that “... scientists will tease out the genes that go afoul in mental disease, if only they are meticulous in their hunt” (Angier, 1993). Based on consanguinity studies like those reviewed in this chapter, such psychiatrists are convinced that there must be a genetic cause, so that when no specific gene can be implicated, there must be several genes. It appears that the old abuse of the concept of reduced penetrance to explain away data inconsistent with genetic theory has now been replaced by reliance on a faith in “polygenetic transmission” to deal with contradictory or inconclusive results (Bader, 1990).

A still more recent genetic marker study (which also made the front page of *The New York Times*) will be discussed later in the chapter, along with alcoholism, in the section on neuropsychological-neurophysiological findings. In addition, some pedigree studies of psychiatric syndromes not yet addressed will be evaluated, within the context of discussing these particular syndromes.

Pharmacological Response

One line of inquiry into the etiology of a psychiatric disorder is *pharmacological challenge*: determining whether any drug can incite the condition, taken to imply that some chemically similar internal hyperfunction is the biological cause of the condition. Another related line is *psychopharmacology*: determining whether there is a therapeutic effect from administration of a drug, taken to imply that the drug must be compensating for an internal deficiency (or countering a hyperfunction) that is the cause of the condition. These approaches taken together comprise the research methodology of *pharmacological response*; they both share the assumption that psychiatric dysfunction has a biochemical basis (probably involving neurotransmitters), with the corollary that drug treatments can be developed to correct homeostatic dysregulation and thus restore mental health. The most obvious problem in this conceptualization is biological reduction-ism-the attribution of psychological symptoms not to past or present environmental events but to some putative bodily abnormality. The rather simplistic designation of “biochemical imbalance” as the cause of mental disorder has become an unfortunate characteristic of con-temporary theorizing in biological psychiatry, usually with the main supportive evidence being response of some patients to a medication. For the general public, the concept of biochemical imbalance dispenses even with that evidence (see Mankoff’s cartoon below). Lipowski (1989) found the concept to be counterproductive, both in terms of its effect on treatment and its narrowing of the scope of scientific thinking:



“Oh, yeah? Well, I think you’re the one with the biochemical imbalance.”

Source: Drawing by Mankoff; © 1992, *The New Yorker Magazine, Inc.*

Another current fad is to tell patients that they suffer from a chemical imbalance in the brain. The explanatory power of this statement is of about the same order as if you said to the patient: “You’re alive.” It confuses the distinction between etiology and correlation, and cause

and mechanism, a common confusion in our field. It gives the patient a misleading impression that his or her imbalance is the cause of his or her illness, that it needs to be fixed by purely chemical means, that psychotherapy is useless, and that personal efforts and responsibility have no part to play in getting better. To assume that biochemical processes underlie mental activity and behavior does not imply that they are causal agents but rather constitute mediating mechanisms. They are influenced by the information inputs we receive from our body and environment and by the subjective meaning of that information for us. It is that meaning which largely determines what we feel, think, and do. This is not to deny, of course, the importance of . . . biological factors for the way in which we respond to information and how it affects us for better or for worse (p. 252).

The psychopharmacological method has also been criticized for *ex juvantibus* logic (Bignami, 1982) because it argues from the effect of a drug backward to the cause of a condition—a deductive error; no drug has a single site of action. The method of pharmacological challenge has its drawbacks too: disparate drugs can sometimes induce the same condition, as can purely psychological interventions, sometimes with-out any known hyperfunction occurring. In fine, although certain drugs can induce behavioral symptoms, and certain medications can alleviate behavioral symptoms, it may be grossly improper to reason from pharmacological-response experiments that behavioral symptoms are the consequence of innate biochemical determinants. Lader (1990), a leading authority in the area of pharmacological-response research, has warned the field about reductionism, although he believes valuable clues to etiology can in some instances be gained:

When pharmacological treatments are deemed effective for a psychiatric condition, a stimulus is given to biological research. Although few are so unsophisticated as to aver that if a condition is helped by drugs, it must be biological in origin, most would accept that biological mechanisms are involved in some way. Working out how a drug ameliorates a certain condition will not necessarily tell us much about the etiology or even the pathogenesis - but it might! (pp. 150-151)

Pharmacological Challenge

The experimental induction of psychosis in animals or humans has a long history (Munkvad, Fog, & Randrup, 1975). As reported by Munkvad et al. (1975), in 1845, Moreau de Tour described the mental effects of hashish; in 1927 Berger reviewed the literature on mescaline, comparing its effect with symptoms of schizophrenia; and in 1931, De Jong produced experimental catatonia in different animal species by means of mescaline. Bercel (1960) reported on the bizarre web-weaving of spiders who had been exposed to schizophrenic blood serum. More recently, LSD has received considerable attention as a “psychotomimetic” drug (Hollister, 1968), as have amphetamine and cocaine (Snyder, 1977). Claims were made that drugs that drive up dopamine levels were repeating the natural action of the brain in schizophrenia, but speculations as to the pharmacological properties of drugs inducing paranoialike symptoms have so far not led to any breakthrough in schizophrenia research. It remains a question as to how relevant “model psychosis” phenomena are to clinical cases. For example, Hollister (1968) showed that clinicians can readily distinguish between drug states and schizophrenic reactions based on mental status examination, and Bleuler (Lipton, 1970) concluded that psychotomimetic agents have contributed to our understanding of organic psychosis, not schizophrenia. A neurotoxic theory of schizophrenia must also deal with the fact that model psychosis can be experimentally induced by sensory deprivation—a purely environmental variable (Schultz, 1965). All that model psychosis research amounts to at this point in time is that toxic substances can cause psychosis, but not that psychosis is caused by toxicity.

Oddly enough, neurosis, not psychosis, has offered an opportunity for the most interesting developments in the area of pharmacological challenge. For example, the experimental induction of panic disorder by administration of sodium lactate will be addressed in some detail in a later section on biochemical correlates of emotion.

Psychopharmacology

Since the advent of the phenothiazines in the 1950s, research has focused on why antipsychotic medications are therapeutically effective. Kety (1975) summarized the early thinking by noting the inverse relation between therapeutic potency of the phenothiazines and the Parkinsonian side effects: it appeared that pharmacotherapy for schizophrenia exacerbated Parkinsonism, and pharmacotherapy for Parkinsonism exacerbated schizophrenia. This observation, however oversimplified, inevitably led to the implication of dopamine in the biochemistry of schizophrenia, and intense investigation has been generated to the point where a dopaminergic hypothesis is now widely regarded within biological psychiatry as an established “finding” in the etiology of schizophrenia. Although it has been shown that phenothiazines block CNS receptor sites activated by dopamine, this still doesn’t necessarily mean that schizophrenia is a biochemical disease; no phenothiazine does more than alleviate certain acute symptoms. Psychopharmacological research is intrinsically

limited: it can be no more specific than the therapeutic value of its drugs. Hence, the scientific standing of the dopaminergic hypothesis cannot be better than ambiguous at this juncture. It is also clear that even if dopamine is proven to be involved, it is involved as well in every kind of human behavior and is always just part of a very complex neurotransmitter story.

Despite vigorous laboratory investigation, no psychiatric disorder has thus far been “cured” by medication, not even manic disorder where lithium treatment has been so helpful. In the area of depression research, van Praag and Korf (1975) declared the findings concerning antidepressant medication have failed to revolutionize the treatment of depression, despite the information gained on relationships among metabolism, mood, and motor activity. In the metaphor of Akiskal and McKinney (1975), we now know something about the “pharmacological bridge” from metabolic events to behavioral symptoms, but we are still largely ignorant about reverse traffic on that bridge, from metabolism backward in time to precipitating psychosocial stressors.

Research on the efficacy of medications is expected from contemporary psychiatry, and biological psychiatrists have responded by developing an advanced psychopharmacology. But the “fishing expedition” of using response to medication as an index to the biochemical etiology of a disorder is inefficient and, worse yet, can get us lost at sea. The efficacy of a drug does not prove that a particular mental disturbance is biochemically determined. For example, aspirin relieves headaches but no one contends that headache is brought about by “aspirin deficiency.” In-stead, we classify aspirin as an analgesic, thereby suggesting that the troubles of the day may prompt a headache, but chemical relief only comes via reducing sensitivity to pain. Analogously, an agitated patient may be helped by a drug that renders him or her relatively lethargic; or, more precisely, the staff dealing with an agitated patient may be helped by a drug that renders the patient more manageable, with the patient benefiting secondarily (I have seen Thorazine used in this manner). In the final analysis, although there is always a somatic process between stressor and symptom by which a drug intervenes to improve a patient’s functioning, the therapeutic effect of a drug can be indirect or even unrelated to the cause of the condition. In other words, pharmacological-response research has a key role to play in biological psychiatry, but it need not create a theory of biochemical imbalance to do so.

Neuropsychological-Neurophysiological Findings

On a visit to America, Bertrand Russell came as a guest to a philosophy class taught by Morris Cohen at the City College of New York. The two men fell into dispute over inductive logic. To make his case, Russell invited the class to disprove the following proposition: There is a rhinoceros in this lecture hall. The students proceeded to turn up desks, peer into closets, and ferret out crevices-but they could not lay their eyes on any rhinoceros. Russell was nonplussed for, according to him, it was not yet certain no rhinoceros was present in the hall; the search must go on. Russell’s position was that inductive logic is an endless process that may never finally prove or disprove an inference. Common sense must somehow then intervene to set a limit and force a resolution.

This story may be apocryphal (like the rhinoceros; I can find no substantiation of its existence in the biographies of either Russell or Co-hen), but its point is well taken. The philosophy of science must take into account that many a “scientific” hypothesis lies beyond confirmation or refutation, until common sense at last calls a halt to infinite speculation and inconclusive research. In this vein, critics of biological psychiatry can point out that here is a discipline that never seems to question its supposition that each psychiatric disorder has a somatic substrate that at least in part causes it. Medicine may not yet know what it is, but it’s looking for it and, by God, *will* find it! The history of biological psychiatry can be depicted as a tale of “promising” leads, closure on slender evidence, hyperbole as initial reception to new work, and ultimately unproductive results. With each failure, however, the faith remains undaunted, simply shifting direction in its quest by optimistic lurches from one new idea to another. Heuristically, a lot of research has been generated but, following about a century of effort, a harsh assessment would be that no substantive results have been tendered for the pathogenesis of any major psychiatric disorder. From this unfriendly perspective, it will appear that the time must soon come to stop a futile hunt for what by now might be presumed to be a non-existent rhinoceros.

In defense of biological psychiatry, it can be replied that the problems studied are complex and it is reasonable to anticipate delays and setbacks before medicine can identify constitutional mechanisms involved in “mental illness.” The lack of definitive answers does not mean that there never will be answers or that the task is a pseudo-problem. Moreover, biological psychiatry will insist that considerable progress has already been made in tracing out the pathogenesis of disorders such as schizophrenia and panic attacks; even more progress can be expected in all areas under investigation if current or future research leads pan out. The herculean labors expended on the totality of projects, both planned and heuristic, will be well worth the effort if we can eventually fix the body as a means to fixing the mind.

All that can be done at present to resolve this quandary in how to evaluate the very foundations of biological psychiatry is to review

syndrome-by-syndrome what biological psychiatry has to offer. We will next take a look at psychopathy, alcoholism, and schizophrenia as sample topics in the search for organic factors underlying psychopathology. We will then critique the findings of biological psychiatry from the perspectives of sociology and psychodynamic psychology, to get some sense as to whether such psychosocial approaches can interpret the data more plausibly.

Psychopathy

Antisocial behavior has been the subject of intense medical investigation for some time. As Hare (1970) described the general approach, “Most of the research on psychopathy is based on the assumption that there is a physiological basis to the disorder. If we could establish that psychopaths differ from other individuals on some physiological variable, this variable might be used as one of the defining characteristics” (pp. 27-28). Thus, the attribution of antisocial behavior to some physical abnormality has led to laboratory research on criminal populations; the history of such research is usually dated back to the nineteenth-century work, in Italy, of Cesare Lombroso, who gave the following account of his experiments:

In 1870 I was carrying on for several months researches in the prisons and asylums of Pavia upon cadavers and living persons in order to determine upon substantial differences between the insane and criminals, without succeeding very well. At last I found in the skull of a brigand a very long series of atavistic anomalies, above all an enormous middle occipital fossa and a hypertrophy of the vermis analogous to those . . . found in inferior vertebrates. At the sight of these strange anomalies the problem of the nature and of the origin of the criminal seemed to me resolved; the characteristics of primitive men and inferior animals must be reproduced in our times. (Wilson & Herrnstein, 1985, pp. 72-73)

Lombroso branded about 40% of the criminals he studied as incorrigible, ascribing their illegal acts to predisposition based on an irresistible “criminaloid” heritage. He distinguished between these “born” criminals (distinguished by such stigmata as sloping forehead, long arms, prognathous jaw, large incisor teeth, and so on) and “occasional” criminals (normal men driven by desperate or passionate circumstances). Lombroso then developed rating scales for criminal propensities based on his anthropometric calculations, but he also could explain away any case of criminal behavior that did not fit into his “atavistic” mold simply by referring to some precipitating situational trauma. By the turn of the century, Lombroso’s data were hailed throughout the Western world as the first “scientific study of the criminal” (Wilson & Herrnstein, 1985, p. 74) because physical measurements and norms were involved!

Ironically, it was precisely the anthropometrics that, in the end, brought Lombroso’s theory down. Critics pointed to the inaccuracy of his anatomical descriptions and the biases of his sampling methods. Subsequent research did not show correlations between “primitive” physical characteristics and criminality. In addition, social criticisms were telling: the so-called “inborn” inferiority of his criminals ostensibly derived from their constitutional heritage but it was obvious they were circularly being called inferior because they were criminals. Racist aspects were also evident in Lombroso’s view of criminals as phylogenetically lower creatures similar to aborigines whom he deemed unable to live up to the standards of civilized Europeans; he proposed to pack Italy’s criminals off to penal colonies in Africa (not only where they “belonged” but also where their rough ways could be utilized to exploit natives on behalf of the imperialist mother-country). In addition, Lombroso’s findings had a sinister effect on the courts and prisons of Europe during the late nineteenth and early twentieth centuries. In the 1899 novel *Resurrection*, Tolstoy has one of his characters, a prisoner in Czarist Russia, ask: “Why and by what right does one class of people lock up, torture, exile, flog, and kill other people, when they themselves are no better than those whom they torture, flog, and kill?” (Tolstoy, 1946, p. 403). The questions asked in the novel by officials in the criminal justice system were of a quite different order: Do some human beings lack the free will to abstain from crime? Could criminal propensities be detected by measuring the skull? What part does heredity play in crime? Is there such a thing as congenital depravity?

Further unproductive efforts to derive criminality from bodily traits were made by Goring (1913), who catalogued physical defects among English prisoners (but dropped “atavistic” implications), and Sheldon (1940), who correlated antisocial personality with “mesomorphic” body build. Eventually, diagnosis based on physical appearance was abandoned, and biological psychiatry used advanced technology to focus on more subtle physiological defects. For example, Hare (1970) presented evidence showing “maturational retardation” in that the EEG readings of psychopaths resembled those of children; he also cited findings of autonomic hypoactivity to account for psychopaths’ lack of anxiety, failure to learn from painful experience, and thrill-seeking. However, such ventures into neurophysiological etiology have not led to the specification of any biochemical flaw or even of the brain subsystem involved; instead, these ventures usually retreat to evidence from pedigree studies that some such defect must exist. A somewhat recent reincarnation of Lombrosian theory took the form of a briefly popular hypothesis that an XYY chromosomal anomaly produced “supermales” who could not contain their aggression (Jacobs, Brunton, Melville, Brittain, & McClellmont, 1965). The designation of the cytogenetic XYY

as a criminal stigma has since been exposed as a myth (Borgoankar & Shah, 1974), and Hare held the same viewpoint-on the grounds that it was not a heritable condition, as his literature review proved psychopathy must be!

Cloninger (1978) summarized the case for psychopathy as a heritable condition, referring to the fact that MZ twins have higher concordance rates than same-sex DZ twins, as well as to a favorable Danish adoption study by Mednick, Gabrielli, and Hutchings (1984), but he too could hardly venture a guess as to just what biological property is genetically transmitted, other than to make a passing reference to the reticular formation as a possible site of defect. Cloninger did not critically evaluate the research that supported his own pro-genetic position, but he did discount a contrary Swedish adoption study because subjects were included whose criminal behavior was deemed secondary to alcoholism. Had Cloninger been more universally critical, he might not have missed a much more damaging flaw in the Danish paper whose conclusions he accepted: Mednick et al. state that only 25% of their criminal sample were adopted immediately after birth, 51% were adopted within 1 year of placement in an orphanage, 13% within 2 years of placement, and 11% after 2 years. In addition to this damaging admission of what appears to be selective adoption in Denmark, the research team reported in a comment located in the "References and Notes" section (p. 894, #11) that a statistically significant association was found between later criminality and length of time waiting for adoption!

They then wondered if this association could be due to the deleterious effect of prolonged institutionalization and whether youngsters from a less desirable family genealogy were harder to place. In short, in a note amid references placed after the conclusion of a paper that argued for genetic etiology in psychopathy, these authors acknowledged that the results of their study could have been produced by a combination of selective adoption and the emotional harm inherent in an extended institutional placement.

Sociological criticism of biological approaches to criminality often bores in on the issue of "classism" in psychiatric diagnosis. For example, Cloninger (1978) declared that although nearly all sociopaths are or become criminals (whether or not legally identified as such), "so-called white-collar criminals seldom if ever suffer from antisocial personalities" (p. 97). As with Lombroso, it appears that there are still two kinds of criminals-shall we say "uncivilized" and "civilized"-and only the former is authentically antisocial in the eyes of biological psychiatry. In contrast, sociologists sneer at the presumption that white-collar criminals, as property owners, will only rarely be psychopathic; the position taken in sociology is that class structure and diagnostic bias, not biological variables, account for the label's use. For example, the "muckraker" movement in America in the late 19th and early 20th centuries depicted the leading businessmen of the day-Gould, Rockefeller, Morgan, and others-as "robber barons" who made their for-tunes by illicit means but were able to manipulate the political system to thwart prosecution. In other words, given enough social success and clout, one man's psychopath can be transformed into everyman's financial tycoon. It also appears that even the "uncivilized" type of psychopath may still have a redeeming social function; thus, Cleaver (1967) has contended that the street criminal redistributes wealth, sometimes with a rudimentary revolutionary consciousness.

Another bone of contention for sociology is the claim, often advanced by biological psychiatrists, that genetic "predisposition" exists for many disorders, including psychopathy, which environment only activates. Clinard and Meier (1975), specialists in the sociology of deviance, found assertions of this nature unacceptably ignorant of social factors and even unscientific, declaring:

Some biologists still believe that crime, alcoholism, certain types of mental ill-ness, and certain sexual deviations can be carried as a specific unit in biological inheritance.... Deviant behavior cannot be hereditary ... since social norms that are directly related to deviant behavior cannot be inherited. Such a theory of inheritance assumes that what constitutes disapproved behavior is the same in all societies and throughout time.....Two leading authorities in the field of criminology [Sutherland & Cressey] stated that it is "obviously impossible for criminality to be inherited as such, for crime is defined by acts of legislature and these vary independently of the biological inheritance of the violators of law." (p. 31)

Psychodynamic interpretations of psychopathy focus on early experience as decisive for character formation. A "superego lacuna" (John-son & Szurek, 1952) may be the result of identification with antisocial parents who raise their children in accord with their own rather than the community's ethical standards. Social learning theory (Bandura, 1973) points to financial rewards for antisocial behavior, inconsistency in discipline, and, especially, aggression modeled by parents, peers, and mass media. Stierlin (1974) looked at family factors, referring to "delegated" children who are often prematurely thrust out of the home to vicariously act-out their elders' forbidden wishes. Bowlby (1951) has written about the "affectionless psychopath" who is unable to empathize and turns against society because of severe maternal deprivation in early years. In the psychodynamic approach, emphasis is placed on how the immediate family and community have failed the child; bio-logical variables are viewed as not particularly pertinent to the genesis of the condition.

In review of the cross-disciplinary data, it is my opinion that biological psychiatry has not yet sufficiently come to grips with

social sciences data according to which “criminality” may have more to do with norms, identifications, and values than with any biological “propensity.” Sociology has primarily pointed to the inequalities of economic opportunity as the cause of crime; psychology has stressed crucial socialization experiences with parents and peers. Indeed, an integrated psychological-sociological perspective may well constitute a totally ad-equate etiological formulation. In connection with the issue of classist bias, the notion that a “biological marker” exists for a diagnosis that turns, in many respects, on a moral or legal judgment, usually made by those more privileged of those less privileged, appears innately im-plausible. Therefore, it does not surprise me that research results in this particular area of biological psychiatry can be considered negligible thus far.

Alcoholism

Alcohol addiction has long been suspected of having some biological component which, in conjunction with opportunity and cultural pressures, causes a “disease.” Jellinek (1960) defined alcoholism as a progressive condition characterized first by psychological and then by physiological dependence; Zwerling derived a typology of alcoholism from the DSM-II psychiatric nosology (Block, 1965). However, the disease model has been attacked because it is not clear whether alcoholism is (a) the disease itself or only a symptom of a personality disorder, or (b) is a mental or a physical defect (Clinard & Meier, 1975). In addition, the voluntary nature of behavior that leads to addiction makes alcoholism non-homologous to any other medical syndrome.

According to Thio (1978), the search for a biological marker for alcoholism had yielded eight different theories put forth by the American Medical Association:

1. Metabolic disturbance;
2. Abnormal sugar metabolism;
3. Endocrine deficiency;
4. Dietary deficiency;
5. Liver deficiency;
6. Sensitivity to food;
7. Dysfunctional “alcohol appetat” in the hypothalamus;
8. Imbalance of the acetylcholine and receptor sites in the ascending reticular formation.

After reviewing the many different and confusing theories, Madsen (1974) concluded that alcoholism is a stress disease; nevertheless, he too compounded the chaos by speculating that it was caused by some sort of dysfunction in the pineal gland. Krimmel (1971) noted several more inconclusive or contradictory constitutional theories not mentioned by Thio, such as missing chromosomes and lowered blood chloride levels; he then quoted Mark Keller, then editor of the *Quarterly Journal of Studies on Alcohol*:

Evidence for physiological addiction has never been produced. The evidence for cell metabolism has not been produced. A tough-minded pharmacologist, has called these notions of altered cell metabolism and physical dependence “exercises in semantics or plain flights of imagination.” (Krimmel, 1971, p. 49)

Further, although Keller was fully aware that there are marked physiological complications in alcoholism, he knew of no research data that proved they were present before the onset of heavy drinking. In a similar vein, Thio (1978) observed that biological researchers often tend to confuse cause with effect:

When they discover that alcoholics are more likely than non-alcoholics to have dietary deficiencies or glandular dysfunction, the researchers assume that these physiological defects are the causes of alcoholism. . . [But] the frequent and heavy consumption of alcoholic beverages is bound to have a damaging effect on the physical constitution. (p. 334)

A notable recent effort to identify a biological marker has pinpointed slight elevations in acetaldehyde levels in the blood of alcoholics after drinking, as compared to controls (Schuckit & Raynes, 1979). Schuckit (1984) has argued that enzymatic mechanisms controlling ethanol metabolism are hereditary and thereby create a biochemical predisposition: higher concentrations mean that the body breaks down ethanol more slowly, making ingestion more pharmacologically potent, causing more organ damage, and leading the at-risk individual to experience inebriation as less impairing. Schuckit is duly cautious in the light of measurement problems in biochemical research and the complexities of ethanol absorption; notwithstanding, his theory must be considered speculative-the validation of his

findings can only come from a *prospective* study based on enzyme samples taken in childhood, predicting who will become alcoholic later on and who will not. But he published long before this could be done, and, so far as I know, it has not yet been done.

Because the pathogenic constitutional agent still remains to be identified, biological psychiatry has in the meantime relied on evidence that alcoholism is a genetically transmitted disease. Some pedigree studies are widely cited as conclusive: Goodwin, Schulsinger, Hermansen, Guze, and Winokur (1973) and Goodwin et al. (1974) and Schuckit, Goodwin, and Winokur (1972). The former is an adoption comparison using the Danish files from the schizophrenia series to identify a cohort of males adopted soon after birth, all of whom had a biological parent hospitalized at some point for alcoholism; a control group consisted of matched adoptees without a biological parent known to be alcoholic. The subjects were interviewed at an average age of 30 by a Danish psychiatrist who was blind as to whether they were probandi or controls; the subjects themselves did not know they were participating in an adoption comparison study and volunteered no information indicating whether they knew their birth parents were alcoholic. As for results, *all* subjects were found to be moderate to heavy drinkers. There was no significant difference between the two groups at any level of drinking, except for the extreme category “alcoholic” (10/55 probandi, 4/78 controls), leading the investigators to conclude that only alcoholism *per se* (as distinct from “heavy drinking”) is heritable. Psychopathology in general was rampant in the series of adoptees, running about two-thirds of both groups based on the clinical impressions of the Danish psychiatrist, so that no difference was observable there. The only other difference was found to be in divorce rates (the probandi were three times more likely to end their marriages). Goodwin et al. (1973) made the following incidental comment: “Divorce and alcoholism have often been associated, but the former has generally been attributed to disruptive effects of the latter. Our data suggests that divorce and alcoholism may perhaps be co-variants of a single or related genetic predisposition” (p. 242). Talk about neo-Lamarckism: it seems even acquired legal status can be inherited these days!

The Danish pedigree study has generally been accepted without demur (Mendelson & Mello, 1979; Rutstein & Veech, 1978). However, in terms of its methodology, the tables in this chapter seem to indicate that 1 or 2 subjects were switched without explanation from the control to the index group, and 4 controls were admittedly added at the end and were not blind to the Danish psychiatrist. This latter procedure is, of course, scientifically unacceptable, especially in view of the fact that the reader is given no information as to what the particular disposition in the study turned out to be. Thus, there is already room for suspicion as to investigator bias and statistical loading. In addition, it is impossible to know just what the probandi heard about their birth parents: they were not asked. Further, if the mother of a proband was the alcoholic parent, there is the possibility of neurological damage in utero and of fetal addiction. And, as always, the question of selective adoption comes up, with “undesirable” children going to less satisfactory foster homes—a possibility the coauthors acknowledged.

Schuckit et al. (1972) compared male probandi diagnosed as alcoholic to their half-siblings, with whom they may or may not have lived. Because most of these subjects came from broken homes, it was also possible to study the relative impact of an alcoholic biological parent vs. an alcoholic surrogate parent (defined as a new spouse with whom the child lived for at least 6 years prior to age 17). The subjects were significantly more likely to be alcoholic if their biological rather than their surrogate parent was alcoholic. Contrasting 32 alcoholic subjects with 132 non-alcoholics, it was reported that 62% of the former had an alcoholic biological parent, compared to only 20% of the latter. Simply living with an alcoholic surrogate parent seemed to have no relationship to the development of alcoholism.

In criticism of this study, the probandi were state hospital patients (thus, in today’s parlance, likely to be MICA patients) who came from unstable families acknowledged by the coauthors to be extraordinarily rent by divorce, remarriage, and re-divorce. It is difficult to believe that these subjects can be considered representative of alcoholics in general. Beyond sampling problems, the study’s design does not even permit blind interviewing. Information concerning alcoholic elders must come from the subjects themselves, as elicited and evaluated by the interviewer. As a member of the research team, the interviewer can hardly be considered unbiased. This questionable experimental design is credited by the coauthors to, of all people, Rudin! It is a contemporary application of his discredited “science of psychiatric genetics,” with the only change being that nowadays we would speak of “genetic pre-disposition” rather than “taint.”

Aside from these troubling issues around Schuckit et al.’s research design, concordance rates for alcoholism are consistently higher for half-siblings raised apart than those raised in the same home, a fact that can be interpreted to mean that half-siblings from a hard-drinking father are more apt to be alcoholic than half-siblings from a non-drinking mother (the fathers were usually the alcoholics and the mothers usually had custody). The data do not include comparison of half-siblings by a common alcoholic parent as opposed to half-siblings by a common nonalcoholic parent, to determine the effect on children when the custodial parent is the alcoholic. Finally, as the authors realized but had no way to control for in the study, the mate of an alcoholic may have alcohologenic qualities that influence both choice of a partner and the way children are raised.

A genetic marker study for alcoholism was reported on the front page of *The New York Times* on April 18, 1990. In an article published in the *Journal of the American Medical Association*, Blum et al. (1990) studied brain samples from 35 deceased alcoholic individuals and 35 nonalcoholic matched controls. They found that the presence of the A1 allele of the dopamine D2 receptor gene correctly classified 77% of alcoholics, and its absence correctly classified 72% of non-alcoholics. They concluded that the gene that confers susceptibility to “virulent alcoholism” is located in the q22-q23 region of chromosome 1}. Noble, the second author of the study, was optimistic about replication: he held that (a) the dopamine receptor was a likely candidate because it has been strongly associated with the brain’s reward mechanisms, and (b) environmental stresses account for only 30 to 40% of the etiological variance of alcoholism (Adler, 1990). Incidentally, this latter estimate is more generous in terms of environmental causation than that of Cloninger and Reich (1976), who claimed that the genetic factor in alcoholism accounted for 90% of the variance.

Unlike the enthusiastic reception we have seen accorded to previous genetic marker studies on depression and schizophrenia, the alcohol study drew immediate criticism. In an accompanying editorial in the same journal issue, Gordis, Tabakoff, Goldman, and Berg (1990) expressed skepticism that the results would be replicated, noting that no one gene would likely cause alcoholism, the sample size of the study was too small, and sketchy information was provided on the matching of controls, as well as on how “virulent alcoholism” was de-fined (the index subjects died of a variety of diseases and were only retrospectively diagnosed as alcoholics). The editorial recalled the re-cent failures to replicate genetic marker studies in depression and schizophrenia, as well as the Egeland retraction, and warned that validity of conclusions in this type of research often hinged on subtle statistical considerations and the stability of the subjects’ diagnoses over time. Although interested in the Blum et al. results and awaiting further findings, the editorial writers even decried biological reductionism in the alcohol study, pointing out that the real research challenge is how genes and environment interact to produce alcoholism in any individual. Such a high level of critical sophistication demonstrates that the field of biological psychiatry is finally learning from the bitter lessons of the past, although there is still unswerving commitment in this editorial to the idea that alcoholism has some genetic component.

Another critique of the Blum et al. study came quickly from Peele (1990). He observed that the article was accompanied by press releases, a highly publicized news conference in Los Angeles, and video inter-views with the study’s authors, which the American Medical Association arranged to have transmitted by satellite in its weekly television news release. In Peele’s estimation, such public relations hype in no way enhanced the scientific value of the study, which still left vague the actual physiological mechanisms involved in alcoholism and which seriously underestimated the importance of social factors. Peele complained that American researchers typically ignore the work of Robin Murray, the leading British expert in the genetics of alcoholism; Murray found no difference in rates of alcoholism for MZ and DZ twins, effectively ruling out a genetic hypothesis if these results are replicated by other researchers.

Gelernter, Goldman, and Risch (1993) reviewed nine studies replicating Blum et al.’s hypothesis linking the A1 allele on the dopamine D2 receptor to alcoholism and found no confirmation—indeed, there was more heterogeneity between studies than between subjects and controls! Thus, on empirical grounds, the spectacular discovery of a gene for alcoholism has been laid to rest.

As for criticism coming from outside the mental health field, sociologists often take umbrage when psychiatric theories posit that organic predisposition is necessary for the development of alcoholism. Clear-cut data tie alcoholism to such social variables as sex, class, ethnicity, and occupation; this research can be synthesized to form a concept of social role already sufficient to account for differential rates of alcoholism. For example, Trice (1966) compared Irish and Italian drinking patterns, noting that the former tended to try to outdrink each other in bars, while the latter imbibed mainly in family settings around meals; the outcome of these disparate patterns was far greater alcoholism among the Irish. Pittman and Gordon (1958) held that, in many cases, alcoholism could be considered an “occupational disease.” They looked at the communal functions of drinking on certain jobs such that every employee became susceptible to eventual addiction through ritual after-hours competitive drinking with buddies, uncomplicated by food or mixed company:

The Army, the Navy, the work camp, the railroad gang, and the lake steamer, all are rich in drinking culture. In these groups the harsh, monotonous routines are broken by the nights, weekends, and lay-offs which offer opportunities to drink. Drinking is a preoccupation and conversations are filled with talk of drink. The all-male drinking group [becomes] a symbol of manliness and group cohesion. (p. 67)

World rates vary enormously, creating a nettlesome problem for any predominantly constitutional explanation. Social factors appear to be decisive; for example, immigrant groups coming to America tend to have much higher rates here than in their native lands, even when opportunity to drink was available in the old country. Fort (1981) has written that the United States is preeminent among nations

as a breeder of addicts, hypocritically pushing a variety of drugs, legal and illegal, for pleasure or relief.

Psychodynamic and family therapists are usually as adamantly op-posed to the disease model as is sociology. Fox (1967) pointed out that a biological predisposition to alcoholism was still not demonstrated:

In spite of the fact that 52% of alcoholics have one or both parents alcoholic we do not yet have proof that there is a genetic disturbance underlying alcoholism. It often "runs in families," but this may merely reflect that a child brought up in an alcoholic home has had a shockingly inadequate family life. (p. vii)

Longitudinal studies of alcoholism, such as that of the McCords (1960), typically show a background of broken homes, economic deprivation, and exposure to heavy drinking. Krimmel (1971) held that alcoholics are vulnerable people by virtue of their disturbed childhood experiences, but this is not to say there is an identifiable "alcoholic personality"; alcohol abuse is viewed by Krimmel as just one more psychopathological reaction to ego damage. Cox (1987) has argued that alcoholism cannot be considered a unitary diagnostic entity; he de-scribed two disparate subtypes: (a) primary (stemming from an im-pulse disorder) and (b) secondary (stemming from stress reduction). Psychoanalytic theories of alcoholism have centered on three themes: (a) oral fixation, (b) repressed homosexuality, and (c) insidious suicide. Research has been notoriously poor in confirming these dynamics, although some findings do show that alcoholics drink to feel powerful (McClelland, Davis, Kalin, & Wanner, 1972), perhaps in reaction-formation to ego-dystonic dependency needs or to compensate for recent narcissistic injury.

Cox (1987) insisted that a total biopsychosocial model of alcoholism would include: (a) biological propensity to alcoholism, plus the effects of drinking on the body before, during, and after addiction; (b) psycho-logical factors, especially counter-dependent needs in which alcohol gives the drinker an illusion of strength; and (c) social factors, such as a "culture of drinking" that pushes at-risk individuals to progressively heavier consumption. To date, the most dubious part of this biopsychosocial model is the assertion about "biological propensity." Again, as was said about the multidisciplinary research on psychopathy, an integrated psychological-sociological viewpoint may well provide a sufficient explanation as to etiology. Biological factors have still to be identified as part of the predisposing etiology, and pedigree studies are not conclusive in terms of genetic factors. However, both common sense and clinical findings dictate that biological variables enter into the clinical equation once drinking starts, and ever more saliently so once the stage of addiction is reached.

Schizophrenia

Schizophrenia has long been regarded by biological psychiatry as a brain disease whose arcane nature must eventually succumb to laboratory investigation. But this assertion has admittedly never been buttressed by solid research findings "until recently"-the usual notation by whatever writer is doing the reviewing at the moment. Smythies et al. (1968) can be regarded as illustrative of this tendency:

For the last fifty years research workers have sought diligently for some bio-chemical or physiological disorder in schizophrenia without, however, until very recently, any noticeable results. Since there was no specific hypothesis to guide research all that could be done was to measure [somatic] variables in schizophrenics and hope by luck to find something abnormal. In this way a great number of investigations were carried out on liver function, carbohydrate metabolism, adrenocortical function, the level of certain cerebral enzymes, the "toxicity" of schizophrenic serum, the mode of reaction to stress, etc. Positive results were claimed from time to time but these were invariably contradicted within a few years. Most of the "positive results" are now known to be due to the fact that the schizophrenics differed from the normal population in respects other than having the illness. (p. 25)

In chastising the field for "hit or miss" research, Smythies et al. believed that biological psychiatry was finally on the right etiological track. They based their optimism on the then-new research on amphetamine-mescaline psychotomimetic effects. Kety (1975) likewise complained that the field seemed very confused when he entered it, but was at last pursuing leads that would provide "light at the end of the tunnel"; the new work he made reference to was the transmethylation studies (which attributed the cause of schizophrenia to the accumulation of hallucinogenic substances in the brain) and psychopharmacologic studies related to the dopamine hypothesis. In neuropsychology, Buchsbaum and Inquar (1982) gave a similar rags-to-riches recitation of the field's history:

A biological test for schizophrenia has so far eluded investigators. Each new neurohormone, each new putative neurotransmitter becomes a candidate. Could it deficiency or excess be the cause of or at least a marker for schizophrenia? Each new electrophysiological test similarly raises the possibilities of the ultimate diagnostic test. The schizotiters and schizowaves are tested on small populations of subjects with excitement, but few receive any wide-spread support. After a time, even their own

developers move on to new transmitters and recordings, abandoning the techniques in the storm of neuroscientific progress.
(p. 235)

Buchsbaum and Inquar then pointed to the latest work on EEG and PET (positron emission tomography)-scans and had no doubt that significant breakthroughs would now occur. Be that as it may, it is interesting to note how they characterized an essentially trendy and serendipitous approach to research in schizophrenia as a “storm of neuroscientific progress.”

Lewontin et al. (1984) panned the assumption within the field of bio-logical psychiatry that schizophrenia must be a biochemical abnormality of the nervous system that will reflect itself in the production of abnormal metabolites in the blood and ultimately be excreted in the urine. This view of schizophrenia engenders “heuristic” studies whereby body materials (urine, blood, cerebrospinal fluid) “from certified schizophrenics are compared with those from ‘control’ normal people with all the assiduity that the Roman augurs used to apply to the examination of an animal’s entrails” (pp. 202-203). They reviewed 30 years of such research:

Among the claims for causative factors in schizophrenia made since the 1950’s we may point to: abnormal substances secreted in the sweat of schizophrenics; injection of the blood serum of schizophrenics into other, normal subjects inducing abnormal behavior; and the presence of abnormal enzymes in red blood cells and blood proteins. . . Conflicting research reports have claimed that schizophrenia is caused by disorders in serotonin metabolism (1955); noradrenaline metabolism (1971); dopamine metabolism (1972); acetylcholine metabolism (1973); endorphin metabolism (1976); and prostaglandin metabolism (1977). Some molecules, such as the amino acids glutamate and gamma-amino-butyric acid, came into fashion in the late 1950’s, fell into neglect, and now, in the 1980’s, have come back into fashion once more. (p. 205)

In a recent co-twin control study, Suddath, Christison, Torrey, Casanova, and Weinberger (1990) compared the size of ventricles in discordant MZ twins. In 12 out of 15 pairs, the schizophrenic member had larger ventricles as well as subtle cytoarchitectural decrements in temporal lobe structures; 7 control MZ pairs did not have this difference. The authors theorized that the schizophrenic twin must have suffered some type of tissue loss, leading to greater intracranial ventricular space, which was either primary or secondary to the disease. They then showed that reduction in brain matter did not correlate with duration of illness so that such morphological change was either simultaneous with or predated the onset of psychotic symptoms. This work has already been hailed as a “landmark” (Goleman, 1990) and is indeed worthy of follow-up in view of the well-established clinical observation that organicity is frequently associated with chronic schizophrenia. However, the validity of the present results is not yet clear: 12 out of 15 cases is not quite statistically significant, the study is retrospective, the reduced size of brain structures is small and not outside normal limits, the crucial issue as to whether such anatomical atrophy is primary or secondary to schizophrenia is still unsettled, and schizophrenic brains do not always have this feature, while normal brains sometimes do (a reversal that occurred in one of the discordant pairs in the study).

Furthermore, in using discordant MZ twins to demonstrate neurophysiological etiology in schizophrenia, biological psychiatry is inherently dis-avowing genetic factors. But it seems you *can* have your cake and eat it too. In a disclaimer, Suddath et al. stipulated that they merely addressed “extragenetic” effects. Despite the fact that they were dealing with genetically identical but nonetheless discordant MZ twins, and found evidence in many cases of post-conception morphological damage in the brain of the schizophrenic member, they still refused to consider that their results, if valid, would effectively rule out a hereditary predisposition to schizophrenia. Instead, it appears they believe that there must be first a genetic predisposition, followed by a subsequent morphological change in brain structure for unknown reasons, to bring about a case of schizophrenia-all this rather than drawing far simpler conclusions from two research approaches that stand in plain opposition!

Cannon et al. (1993) studied developmental brain anomalies in the offspring of schizophrenic mothers in order to investigate ventricular enlargement from another angle. After carefully controlling for the effects of age, gender, substance abuse, and history of organic brain syndromes, they found significant, stepwise, linear increases in cortical and ventricular cerebrospinal fluid-brain ratios with increasing level of genetic risk for schizophrenia in the parent-child cohorts they studied. Their data implicated two interacting factors-(a) genetic loading and (b) obstetric complications-as predictive of later schizophrenia in the offspring. Accordingly, they drew the inference that abnormalities in the brains of schizophrenics are neurodevelopmental in origin and may play a role in the etiology of the disorder. However, their experimental sample was selected based on a diagnostic criterion of “schizophrenic spectrum disorder” and so cannot be extended to “schizophrenia.” A control group was sorely lacking in this research. Data were presented in aggregate form, so one cannot tell whether there were subjects with prenatal ventricular enlargement who later on did not become schizophrenic, or subjects without the prenatal enlargement who did become schizophrenic. Suddath et al.’s prior work on ventricular enlargement in discordant MZ twins is not mentioned, perhaps because that study raises issues that are not compatible with “genetic” findings in this

study. Although the Cannon et al. investigation is indeed suggestive, it still has not been shown that all or most schizophrenics have oversized ventricular space at the expense of brain tissue, or even that morphological changes of this nature lead to psychotic behavior.

The bottom line here is that biological psychiatry still is uncommitted to any definite hypothesis as to the site or mechanism of neuropsychological-neurophysiological dysfunction in relation to schizophrenia. van Praag & Korf (1975) acknowledged that laboratory results have been “meager” and urged that research in schizophrenia should henceforth focus on biological correlates of symptoms rather than diagnosis. Hence, we are left with the conundrum as to whether schizophrenia is essentially a brain disease that medicine will ultimately explain, or whether it may be a psychological condition simultaneously reactive and adaptive to a highly problematic social milieu. At this point, the stance of biological psychiatry is to uphold the diathesis-stress approach, in which a constitutional propensity must be triggered by a noxious environment; as we have seen, this putative “propensity” perforce exists because pedigree studies so indicate.

Sociological criticism of biologically oriented explanations of schizophrenia often has centered on the strong relationship between social class and incidence; a series of investigations, culminating in the work of Hollingshead and Redlich (1958), has demonstrated that poverty is a significant risk factor. Aside from the possibility that diagnosis tends to be more benign when the patient is affluent, the major interpretation of these data is that greater stress faced by the poor contributes to higher rates of mental breakdown. However, Dunham (1977) has reinterpreted the data according to a “downward drift” hypothesis that has been endorsed by many biological psychiatrists (Guggenheim & Nadelson, 1982); Dunham argued that vocational failure by schizophrenics accounts for their relatively disadvantaged socioeconomic standing. Both factors are probably operative, but “downward drift” cannot apply very well to the multitude of schizophrenics who were never “up” to begin with.

Psychodynamic criticism has tended to focus mainly on faulty parenting as a necessary and sufficient cause. The “schizophrenogenic mother” concept was propounded by Fromm-Reichmann (1959, p. 164) and has been supplanted by a more comprehensive theory of family communication deficits that presumably can disorganize and drive the helpless child crazy (Bateson, Jackson, Haley, & Weakland, 1956; Lidz, 1973). Laing (1972) went so far as to suggest that the schizophrenic child may be more sane than the family-of-origin! Clinicians are understandably leery of such an extreme position, but the general approach has been to implicate the parents in the etiology, and even to picture the child as sent on a “mission impossible” to preserve the family, often by remaining with an enmeshing parent. Most of the evidence for the view that family pathology causes schizophrenia comes from clinical casework; however, one can also mention the naturalistic observations of Henry (1971), who lived in the homes of psychiatric patients in order to make anthropological field notes about a milieu he too found very disturbing (but this may have already been his bias). Somewhat firmer data have come from Sobel (1961), who followed 8 cases of children born to parents who were both schizophrenic-4 of these children were raised at home and 4 were immediately placed in foster care. Sobel reported that none of the foster-raised children seemed disturbed after 18 months of observation, but 3 of the parent-reared children were already symptomatic by 14 months. Unfortunately, Sobel did not follow his infant cases to an adult diagnosis, with independent confirmation of his clinical impressions. In a more comprehensive longitudinal study, Tienari et al. (1987) reported that none of the children of schizophrenics who were placed in “good” foster homes became schizophrenic, but most of the children placed in what were previously judged to be “bad” foster homes did develop the disorder in young adulthood. In an unusually detailed study, Greenspan (1987) has shown that children of mothers who were severely impaired by psychiatric disorder were already symptomatic by 3 months of age. Reading Greenspan’s account of the developmental consequences for infants receiving some of the worst possible mothering, one feels sure that these youngsters would be either dead or irretrievably crazy if there had been no clinical intervention. Of the three studies cited-Sobel, Tienari, and Greenspan-the latter two investigations assumed that predisposing genetic factors would adversely influence the psychic development of offspring of schizophrenics, but they concluded that placement in a proper foster home (Tienari) or intense psychiatric support for mother and infant (Greenspan) can serve as suppressor variables. Nevertheless, in all three of these studies, a noxious family environment can arguably be seen as cause enough of severe emotional disturbance in the children; an academic tip of the hat to biological psychiatry may just be *proforma*.

Has biological psychiatry made a strong case for organic etiology in schizophrenia? It is the educated guess, but only a guess, of most clinicians that a constitutional factor probably is involved in schizophrenia, but it is far from clear whether such a factor, if it exists, will prove to be cause or effect, genetic or developmental, neurotransmitter or morphological, and so on. To the credit of biological psychiatry, the re-search effort to date has been formidable, but theoretical findings re-main essentially inchoate, shifting, and speculative, without always admitting this is so. Based on what we currently know, it is still conceivable that a noxious-enough environment could bring about psychotic decompensation without any predisposing bodily vulnerability. As I see it, the current state of evidence in favor of a biological origin of schizophrenia can hardly warrant any dogmatic assertion concerning genetic transmission,

constitutional predisposition, or mode of biological action. An example of such dogmatism is the complaint by Torrey (1983) that family therapists make parents of schizophrenics feel guilty for what he describes as the “biochemical disorder” of their child; he then adds that many families have rallied to his “humane” explanation of the nature of schizophrenia. But what may represent “humane” truth to Torrey and his clientele can be to others mere biological reductionism that takes away human agency; what Torrey has done is effectively take the schizophrenic’s social system off the hook of responsibility for a family member’s tragedy by blaming an impersonal and hypothetical defect in the body of the patient. In any event, the claim that a biological explanation of schizophrenia is more “humane” than one based on psychodynamics or family-systems theory cannot be accepted as validation of the former’s scientific worth.

Comments on the Three Cross-Disciplinary Comparisons

Given that it is not possible to ever disprove some sort of constitutional basis for psychopathy, alcoholism, or schizophrenia, the research efforts to find a “biological marker” will go on. Despite substantial social science data indicating that environment alone could cause any of these conditions, this is as it should be; closure on debate would be pre-mature now. But merely carrying on with biological research does not automatically mean that we will get closer to definitive answers. The answer may be that there is no answer. In all three areas, I have noted the same serendipitous and trendy search to identify some organic factor that presumably causes the condition. A succession of studies then results in “promising leads” that soon get advertised as the long-awaited “breakthrough” in a supposed storm of scientific progress. Thus far, when it comes to organic etiology in biological psychiatry, despite growing sophistication in research methodology, it is, more or less: *Plus (a change, plus c’est la même chose*. I have also noted many assurances in scholarly language that the elusive constitutional mechanism must exist and is just awaiting discovery. Such claims are based on genetic studies that are not subjected to sufficient critical examination, although there may be criticism of contrary findings. Finally, I have noted unwillingness to consider the contingency that social or psychodynamic variables are adequate unto themselves to account for a given psychiatric condition; instead, biological psychiatry tends to insist on an ostensible “biopsychosocial” paradigm in which, as it always seems to turn out, biological factors are prepotent.

Nevertheless, although I believe that purely psychosocial etiology may have to be accepted for some diagnostic categories in the long run, nothing I have said should be construed to mean that any of the three diagnostic groupings just reviewed have already been demonstrated to be psychosocial in origin; any of them might ultimately be shown to have some somatic dimension in its etiology. The present paper cannot dismiss this possibility, no matter how substandard, inconclusive, or contradictory much of the research has been.

Biochemical Correlates Of Emotion

The search for biological markers in anxiety or depressive conditions is especially hopeful in that affective phenomena, by their very definition, must be somatically expressed. Nevertheless, research is complicated because more than psychophysiological processes need to be studied. There are also metaphysical (mind-body) questions to resolve, and they have long stymied human inquiry.

The very first issue is semantic: What is “emotion”? Rapoport declared that we cannot clearly say, because we regard emotion as both a phenomenon and a dynamic (Plutchik, 1962). The term may also refer to conscious or unconscious experience; Freud postulated that dysphoric or ego-alien affect may be masked by defense mechanisms so as to be denied. The debate continues as to whether “primary” emotions exist. If they do, which ones are they and what is their total number (Izard, 1972)? Further, there are undoubtedly physiological correlates of emotion, but it is not certain that this implies any physiological *specificity* (i.e., a characteristic, humanly universal neurochemical sub-strate for each emotion). Still further, controversy has swirled around the causal sequence in emotion: Does a psychological aspect precede and trigger the somatic aspect, or vice versa? The James-Lange theory holds that the body reacts to a perception and this reaction *is* the emotion (in other words, the boy is fearful because he trembles, not trembling because he is fearful). This approach argues that the precipitant is an environmental happening that stimulates the thalamus. “Down-ward discharge” activates the viscera (ANS) and the muscles (CNS) while “upward discharge” subsequently informs the cortex and gives the “feeling tone” of an emotion (Gellhorn, 1964). Such theory offers a process explanation of emotional consciousness (Mandler, 1984) in which some sort of reflex response sets in motion both molecular and molar behavior; labeling of the emotion is a second-order event arising from feedback as to what the body is already doing. Note how the thalamus has replaced the cortex as the “thinker” in this mind-body equation! Refutation of the James-Lange approach was attempted by Cannon (1929), who maintained that even when neurological damage precluded visceral feedback, emotional behavior still occurred; that ANS reactions are too slow to give the cortex much of a clue as to what is “felt”; that patterns of emotional differentiation are not clear; and that, when visceral reactions are chemically induced, no emotional change may follow. An alternative to the James-Lange account came to be called the Cannon-Bard theory; it suggested

that emotions could be experienced without occurrence of bodily changes—all that was necessary was activation of the sympathetic adrenal-medullary system in emergency situations (thereby implicating the cortex as the initiator of the process). Thus, according to Cannon-Bard, cortical functions play a key role in affective states, both in the perception of what becomes exciting and in the interpretation of what the body's response means. In other words, general visceral arousal has to be initiated and structured cognitively to have a distinct emotional experience.

Beyond the semantic problems, the next issue concerns the fact that “emotion” is an evolutionary constituent of the human being; because this is so, we are presented with a phylogenetic puzzle when it comes to “emotional disorder.” Is such pathology normal behavior in the face of perceived stress (although thresholds may be low or perceptions disordered), or does some abnormal physiological functioning make the situation stressful? The investigations of biological psychiatry into anxiety and depressive states have mainly concentrated on the latter possibility, with exhaustive research efforts going into the identification of a distinct biochemical anomaly in the index cases studied. However, if the former possibility is the correct one, all that can be demonstrated by research into the latter is that autonomic reactivity correlates with symptoms, but without any premorbid marker common to those who are subject to the disorder. Moreover, even if biochemical abnormalities were to be found, we still wouldn't know that these “cause” emotional disorders; constitution is a mechanism for affective expression, not a determinant. Biology sets a limit on what behavior can be, but is not able to dictate its content (Costello, 1976). If biochemical abnormality is why some people feel what they feel, mind-body dualism is supplanted by biological reductionism in those cases, and by logical extension in all cases.

A third point of contention arises from nosological groupings of anxiety and depressive conditions into discrete types. Does each subcategory have its own distinctive biological workings and thus respond to different medications, or do the various subcategories share a common genotype but not a phenotype? Indeed, are anxiety and depressive reactions themselves differentiable on a neurochemical basis? Current answers are far from conclusive; they range from insisting that research address each subcategory separately because underlying pathophysiology is different (Paul & Skolnick, 1984) to proposing that genetics are the same for anxiety and depression and only environment makes them different (Kendler, Heath, Martin, & Evans, 1987). Consideration must also be given to the research data of Schachter, who proposed a “cognitive labeling theory” of emotional activation (Schachter & Singer, 1962). This work is consonant with the James-Lange approach in that bodily changes are shown to precede the experience of emotion, but parted from the James-Lange approach in that very similar physiological changes are shown to accompany different emotions, with only the context permitting discrimination on a cognitive level.

As can be seen, the biochemical correlates of emotion provide an inviting field of investigation for biological psychiatry, but an especially difficult one as well. We now proceed to an outline of the contemporary status of research into anxiety and depressive disorders.

Anxiety Disorders

Panic attacks are nowadays widely held to be accessible to a biochemical explanation (Sheehan, 1982):

Until recently panic disorder was viewed almost exclusively in psychological terms. It was believed that the patient was overreacting to a life stress or an “unconscious” conflict. A growing body of evidence now suggests that we reverse this view in favor of a medical-illness model. This model suggests that in contrast to stress-related situational anxiety, panic disorder is associated with a biochemical abnormality in the nervous system, to which there is a genetic vulnerability. (p. 156)

The hereditary aspect of panic disorder is reviewed by Crowe (1984), who summarized research to set a lifetime prevalence rate of 2 to 5%, whereas consanguinity studies showed a morbidity risk in first-degree relatives of up to 61%. Several MZ-DZ twin comparisons indicated much higher concordance in the identical pairs. Thus far, no adoption study has been done in this area. Crowe acknowledged he was unable to proffer definitive data in favor of genetic etiology, although he considered the above-cited statistics as more or less convincing! Torgersen (1983) compared 32 MZ and 53 same-sex DZ twins in Norway and concluded hereditary factors were significant in panic disorder but not in generalized anxiety disorder; however, he applied the “equal environments assumption”—a premise, as we have seen, that is likely not tenable. All told, drawing on only family and twin rates, the genetic investigation of panic disorder is still at a relatively crude stage. As to the importance of genetic factors, Rainer (1976) has cited work that estimated that heredity accounts for 80% of the etiological variance in neurotic conditions, without any evaluation of the experimental procedures.

In the research on specific somatic abnormalities, attention has focused on the chemical provocation of panic disorder through such means as lactate infusion, carbon dioxide inhalation, or administration of yohimbine, caffeine, or isoproterenol, despite many questions

as to which of these drugs has effects most closely resembling the natural phenomenon (Roy-Byrne & Cowley, 1988). In the most successful pharmacological-challenge work ever done in biological psychiatry, intriguing results were reported by Pitts and McClure (1967) in their demonstration of the experimental induction of neurosis in a laboratory setting. They provoked very convincing panic attacks in 13 out of 14 anxiety patients, as well as 2 out of 10 normal controls, through bringing the venous lactate level to a range usually only attained with maximum muscular exertion or after administration of adrenalin. Nevertheless, attempts to use lactate level as the biological marker for panic disorder have failed (Tuma & Masser, 1975): metabolism of sodium lactate to bicarbonate is so swift that blood lactate levels do not elevate following infusion (Grosz & Farmer, 1972), nor has it been shown that levels are higher in premorbid panic disorder patients than in others. Because it is now well established that lactate infusion does precipitate panic attacks, particularly in persons who already have a history, Gorman (1984) has speculated that a panic attack is an adaptive mechanism gone awry: laboratory provocation by lactate or other chemical agent may trigger an anoxia detector, with some people being hypersensitive enough to create a perceived need to flee. For Gorman, the question these days is no longer deemed to be: "What is the biochemistry of panic disorder?" but rather "Why does lactate produce panic?" However, Lader (1990) disagrees, showing that lactate produces panic symptoms only if administration is preceded by appropriate tension-arousing instructions and then only in already susceptible individuals. Moreover, if lactate is indeed a factor in the biochemistry of panic disorder, it can only be as a mediator-specific environmental events (the phobic situation) are the agents that incite a fight-or-flight somatic reaction, and lactate infusion is essentially limited to producing panic in those long familiar with such symptoms (i.e., it is their way of dealing with stress). Thus, sketching in the bio-chemical processes, two phases would be necessary to explain the re-ported experimental findings:

1. A cognitive perception of threat activates the adrenal system, resulting in a release of lactate and a subsequent interoceptive sense of muscular overexertion and oxygen deprivation (a Cannon-Bard sequence);
2. The visceral reaction of "suffocation" feeds back into the perception of threat (a James-Lange sequence).

This hypothetical account still leaves unsettled the problem as to why some people are more susceptible than others to the perception of threat from nonmalignant sources, and such a theoretical gap can perhaps best be bridged by referring to dire associations from one's past as instrumental in setting in motion a psychosomatic alarm-reaction (a psychodynamic sequence). Lader (1991) has offered a very similar but more detailed perspective in which a stimulus is cognitively appraised as "anxiogenic," arousing normal physiological reactions; but, in patients so disposed, a catastrophic interpretation of the physiological changes quickly occurs which triggers yet more anxiety in a feedback loop until a full-blown panic attack is under way. Lader then shows how cognitive therapy at either the perceptual or catastrophic-interpretation stage can prevent the incipient panic, as well as how each of the various anti-anxiety drugs blocks different phases of the physiological buildup in the pathological psychosomatic process. The cognitive-visceral interaction is obviously a great deal more intricate than is indicated by Carr and Sheehan's (1984) conclusion that "panic disorder is a biological disease but one consequence of a primary brain-stem neuronal dysregulation" (p. 107).

Considerable research has also been done relative to other aspects of the biochemistry of anxiety; this work can be summarized as rounding up the usual neurotransmitter suspects whenever there is an investigation. For example, adrenergic receptors, GABA, and catecholamines have been studied with respect to panic disorder, but without substantial results (Hicks, Okonek, & Davis, 1980). Although sympathetic over-stimulation has long been assumed in panic disorder, many findings indicate parasympathetic abnormalities as well, so no simple theory can accommodate all the data (Gorman, 1984). Some work has focused on mitral valve prolapse, but Gorman notes that some panic disorder patients have this defect, although most individuals with this defect do not have panic disorder. To further confuse matters, several books in the "pop psych" literature have categorically attributed anxiety conditions to inner ear dysfunction (Levinson, 1986) or to poor nutritional balance (Marmorstein & Marmorstein, 1979).

Another area for recent research has been obsessive-compulsive disorder. Hollander et al. (1988) used biological challenge in the form of the chemical MCPP (m-chlorophenylpiperazine) on obsessive-compulsive patients, producing an exacerbation of symptoms in the majority; the re-searchers then hypothesized that such patients have overly sensitive serotonin receptors. The research team also found that intravenous injection of the antihypertensive drug clonidine led to reduction of symptoms, suggesting to them that the neurotransmitter norepinephrine moderates anxiety triggered by the disorder. Some difficulties with these inferences are: in model-neurosis designs, a drug may affect many sites of action; it is not demonstrated that afflicted individuals have a premorbidly higher sensitivity to serotonin; and the question is begged as to what causes excess serotonin production as a possible biochemical determinant of anxiety or what causes an insufficient supply of norepinephrine as a possible moderator of anxiety. It is especially troubling that subjects who respond to biological challenge already have an obsessive-compulsive disorder: this could very likely mean that subjects who respond to stress with obsessive-compulsive symptoms do so in laboratory experiments too, rather than that the laboratory

procedure pushes their specific symptom above some putative “biochemical” threshold. Also, it must be remembered that laboratory responses are *not* necessarily tantamount to real-life responses, given that insidious “demand characteristics” are imposed once anyone becomes a subject in someone else’s experiment (Orne, 1962).

Depression

Depression has well-known vegetative signs—a fact that already speaks to a constitutional component in the pathogenesis. However, as was mentioned with respect to anxiety, organic factors may mediate rather than cause the condition, in which case a cognition sets off a psychosomatic chain of events, with bodily activity then feeding back to the cortex, alerting and confirming messages about emotional state. In this conceptualization, a cognitive interpretation that the situation is “bad” initiates CNS and ANS reactions that are both an expression of depression and a signal to the self that something is wrong (i.e., one is depressed). Put figuratively, what I behold upsets me, so I cry; there are tears in my eyes, which shows how upset I am. In such a Cannon-Bard/ James-Lange feedback model, a premorbid biological marker for susceptibility is not necessary, although markers may be found subsequent to symptom onset as a result of chronic reaction, sometimes doing physiological damage in due course. The theoretical approach I am presenting is not one that biological psychiatry tends to endorse; investigations into affective disorders are usually based on a search for distinctive somatic signs that are presumed to be etiologically crucial, represent some kind of biological aberration, and may be inborn. Thus, our review can start with the contention held by many biological psychiatrists - that depression has a genetic basis and that patients with an affective diagnosis are viewed as having inherited a “predisposition,” a latent tendency just waiting to be evoked by some mildly stressful or even ordinary life event.

Gershon (1983) regarded the genetic transmission of depression as a settled issue. In his account of the evidence for heritability, he prematurely intermixed the next issue: what is the pathophysiological vulnerability and what gene or genes are involved? His manifest bias aside, data in support of this genetic thesis start with consanguinity studies, although Gershon acknowledged these are highly inconsistent in re-reported rates, partly because of differences in procedures and criteria and partly because of likely cross-cultural differences in prevalence. Although aware there can be no “true” rate of diagnosable affective illness, Gershon still argued heritability because within-study comparisons show that relatives have higher rates than controls—the old “runs in the family” fallacy. He then cited MZ-DZ twin research to show higher concordance rates in the former group—another methodology that cannot control for environment as an extraneous variable. Gershon did refer to an MZ-twins-reared-apart study (comprising no less than 12 pairs from one country!) but he was leery of its findings because of the lack of systematic sampling. Gershon realized that adoption studies would be essential for any demonstration of genetic etiology, but unfortunately he could point to only one such investigation, dealing with bipolar disorder, which he nevertheless found adequate for his purposes. This is the report of Mendlewicz and Rainer (1977) which, parallel to the Danish adoption studies in schizophrenia, was able to get significant results only by creating an “affective spectrum,” including bipolar, unipolar, cyclothymic, and schizoaffective diagnoses. Working in Belgium, Mendlewicz and Rainer found 31% of the biological parents of adopted bipolar probandi to have “affective spectrum” disorder, more or less comparable to the 26% rate found in parents of home-raised bipolar patients, but significantly higher than the 12% rate found in the adoptive parents. Gershon did not question the validity of this favorable study, but, as always, interpretation of the data was weakened by failure to give any case history information, so that we never know why or when the children were given up for adoption, or whether there were long stays in temporary shelters or institutions before placement. We also do not know whether the children ever knew their mothers were psychiatrically ill (no fathers in their sample were in the “affective spectrum”), nor whether there was contact with the natural mother after placement. Moreover, the mental health of adoptive parents is apt to be better than that of biological parents who lose custody: adoptive parents are screened for mental health before they can receive custody from a foster care agency, whereas biological parents only have to conceive a child and may even have a major emotional disturbance that led directly or indirectly to the placement of the child. Gershon wound up his survey of evidence for the genetic point of view by referring to preliminary data on a collaterals adoption study of suicide; using the Danish cohort from the schizophrenia study, significantly higher rates were reported for suicide in the biological relatives of adoptees who committed suicide than for adoptive relatives (3.9% vs. 0.6%). Schulsinger, Kety, Rosenthal, and Wender (1979) concluded that suicide per se was in part a product of genetic transmission, quite apart from mental disorders (e.g., depression, alcoholism) frequently associated with suicide. This bold deduction stemmed from the fact that half of the relatives, biological or adoptive, were not in any kind of psychiatric treatment at the time of their suicide. Clayton (1983) questioned such logic on the grounds that not being in treatment does not preclude having a psychiatric disorder. Kety’s (1979) interpretation of the same Danish family data was even more problematic: he regarded suicide as a frank product of brain disease. Kety thought research on suicide parallels that once done on pellagra, which was initially found to follow kinship lines without anything more being known about its etiology until Goldberger, in 1915, showed that the

mechanism of transmission was a deficiency in B vitamin niacin. Kety expected neurobiological defects to be discovered for all mental disorders which, for now, can only be said to run in families, without information as to the exact mode of transmission. But Kety's use of pellagra as an analogy for suicide is curious: pellagra has an environmental cause (it "runs in families" because the family eats the same food), whereas Kety insisted that suicide is a hereditary condition. If Goldberger had interpreted family concordance rates for pellagra in the same manner as Kety did for suicide, Goldberger never would have investigated the role of diet! Moving to another dimension of criticism, neither the Kety nor the Schulsinger et al. studies dealt with the theoretical considerations that for suicide to be genetic, a major tenet of evolutionary theory would be violated (survival of the fittest) and the heritability of acquired characteristics upheld (neo-Lamarckism).

As to the biochemical pathology that must underlie depression (and suicide) if the condition is inherited, research has tended to follow the fixed ideas of contemporary biological psychiatry—namely, that abnormalities in neurotransmitters cause behavioral disorders. Although no definite findings have yet been established, extensive research has been done based on pharmacological-response studies because manic-depressive states can often be ameliorated by drug therapy. Schildkraut, Schatzberg, Mooney, and Orsulak (1983) were respectful of the pathophysiological complexities of depression but nevertheless felt confident that the emerging field of "psychiatric chemistry" will discover new medications that will provide clues to the various mechanisms resulting in different forms of depression. These researchers hypothesized that a deficiency in brain catecholamines, particularly norepinephrine, led to depression, whereas an excess led to mania. In recent years, alternative models have held that depressive conditions can be dichotomized as either "noradrenergic" or "serotonergic," and still other researchers have stressed the role of acetylcholine. To complicate matters further, Schildkraut et al. pointed out that depression is a neuroendocrinological metabolic disorder; biological markers may be found in biochemical systems other than neurotransmitters. The problem with current research is not so much the plethora of speculation and the lack of definite findings—it is that most of the work is based on drug efficacy, leading to inferences about the somatic processes by presuming the drugs are supplying a deficiency that causes the psychopathology. This is an unabashed medical-model approach, viewing depression as caused by a specific biochemical dysfunction, distinct for each diagnostic subcategory, and with cognitive as well as situational variables reduced to an epiphenomenon of merely incidental interest.

Summary And Conclusions Of The Critique

Although all research studies have flaws, the present writer believes the literature of biological psychiatry does not come close to meeting scientific standards in terms of methodology. Biological psychiatry must abide by the same criteria for presenting empirical data and drawing careful inferences as any other medical or social science field. This signifies that any studies that do not meet standards for proper re-search procedures or interpretation of data must not be accepted for publication, or if already published must be discredited within the professional literature. Some of the most egregious errors in terms of sloppy procedure are: citation of older papers that lack a methodology section, give no case-history information, violate the canon of "blind" diagnosis, change diagnostic criteria at midstream of a study to get significant results, and offer no assurance of good-enough environment in nature-nurture studies in sampling of subjects. Some of the most egregious errors in terms of sloppy inferences are: including virtually no critique of favorable previous studies, regarding theories as valid before replications or longitudinal results are available, failing to consider alternate psychosocial explanations, predicating human action on grounds of biological determinism alone, and automatically explaining inconsistent results from several studies by invoking, without any empirical basis, such statistical or conceptual artifacts as "incomplete penetrance" or "polygenetic transmission."

In addition to improving the quality of research methodology, it is incumbent on biological psychiatry to strictly acknowledge and respect the limitations inherent in current methodology. We will briefly mention some of the limits we have seen repeatedly trespassed in each of the four types of methodological approaches.

1. In *pedigree studies*, consanguinity rates and MZ-DZ comparisons are not capable in principle of establishing genetic etiology, nor are they "suggestive" in the "right" direction. MZ-twins-reared-apart and adoption research are capable of demonstrating genetic effects, provided that such extraneous factors as selective adoption, inadequate foster conditions, and subsequent contact with biological relatives are controlled for in the experimental design (practically speaking, a difficult feat). All told, when explicit evidence for genetic etiology is lacking, biological psychiatry tends to fall back on implicit evidence such as what "runs in families" or presentation of statistics without case history data. A century after the Jukes book, this is scientifically scandalous and shows the influence of the eugenics movement to this day. As previously noted, we tend to use the parlance nowadays of "genetic predisposition" as a euphemism for "taint," which makes it harder than before to detect any classist or racist bias.

Furthermore, it is alarming just how preposterous biological research can be in accounting for human social behavior on genetic grounds without any questioning of its own methodology precisely because implausible positive findings are reported. For example, consider the use of the co-twin control method by Eaves, Eysenck, and Martin (1989) to investigate the extent to which social attitudes are inherited:

Our study suggests that genetic factors play a surprising role in maintaining human diversity. Even within families, it is clear that dizygotic twins hold religious and political views that are significantly more diverse than monozygotic twins. Given a "religious" home environment, it may still be partly a matter of genotypic predisposition whether one child or another remains faithful to the beliefs of his parents or chooses a more secular philosophy. Many social and accidental effects may intervene between the individual genotype and the final expression in a particular attitude or belief. In our present Western society, however, the probabilities along the way may be biased as much by the genotype of the individual as they are by the social and educational environment to which he is exposed. If this is a good model of human development then we expect a correlation between genotype and social attitudes. If social attitudes play any part in the behavior of one person towards another then we may find that genetic differences between people are partly responsible for the distinction between godly and ungodly and between liberal and conservative. . . (pp. 375-58)

Eaves et al. go on to show that "40% of the variation in [scores on a conservatism scale] is apparently due to additive genetic factors, 30% due to environmental differences within families, and 30% due to differences between families" (p. 360). Beyond the questionable validity of the equal environments assumption in this type of re-search, common sense (plus a bit of knowledge about sociology) might suggest that a co-twin control methodology that leads to such a conclusion about the genetic transmission of political values must have dubious credentials.

The case is no better with the Plomin, Corley, Defries, and Fulker (1990) study of the genetics of childhood television-watching habits, based on the method of adoption comparisons. They found that biological, adoptive, and control (nonadoptive) parents looked at television an average of 5 to 10 hours per week and were not significantly different, although the biological parents soon to give up custody, based on self-report during the last trimester of pregnancy, watched somewhat less. However, the viewing habits of biological parents who lost custody significantly correlated with their adopted-away children's viewing habits at ages 4 and 5 (but not at age 3), so that genetic variance is calculated by Plomin et al. at 34% for age 4 and 30% for age 5. Parent-child correlations were significant but at a higher level in the control families, and significant but at a lower level in the adoptive families. These authors concluded that "individual differences in children's television viewing are significantly affected by genetic factors as well as shared environmental influence" (p. 376), but with only about 20% of the variance accounted for by the environment! Despite impressive statistical analysis and research design in the study, one cannot help but wonder about the validity of these inferences from rather ambiguous data, as well as about what ideological purpose is being served in the course of regarding human habits in genetic terms and thereby generating this particular line of research.

2. *Pharmacological-response studies* assume a neurophysiological imbalance causes a condition; they attempt to provoke the condition by chemical challenge or relieve the condition by medication. The trouble is that sundry drugs can induce the same condition, and the condition may also be induced without any drug. There are other questions: Is the induced condition quite the same as the naturally occurring psychopathology? Are there "demand characteristics" in the experimental induction of neurosis or psychosis for the subject to produce such symptoms? As for medications, even when psychotropic agents work (and they only do to some extent), we do not ordinarily know the site of action of the drug, nor whether the drug acts directly or indirectly on the condition. In summary, although pharmacological-response re-search is pragmatically extremely useful, its theoretical value in relation to etiology is circumscribed in that administration of a chemical may stimulate or inhibit the somatic processes involved in mediating the expression of a behavioral disorder, but without either causing or curing the behavioral disorder.

3. The *search for organic causes* of each type of psychopathology is a "fishing expedition" that generates enormous research and a literature all its own, but without discovering the constitutional basis for any functional disorder thus far. In general, genetic studies are uncritically re-lied on to ensure that an as-yet-unknown constitutional defect must be *there*. However, in this manner, the possibility is discounted that there may be *no there there*! A research approach committed to find some organic dysfunction to account for psychological disorder has a limitation: if environment should be the cause of the disorder, such research will go on *ad infinitum* in a fruitless search because no means exists to check its own assumptions. What's more, such self-perpetuating research will insist all along the way that there is imminent "light at the end of the tunnel"! Only knowledge of alternative social science explanations can make possible an evaluation of biological theories vis-a-vis environmental theories.

Biological psychiatry has been fixated on the premise that a neuro-physiological abnormality accounts for nonadaptive emotional reactions. In so doing, somatic processes are seen as causing rather than mediating behavioral events (as is also the case in pharmacological-response research). Further, short shrift is given to the possibility that emotional experience may be physiologically nonspecific (just representing a state of autonomic arousal that is differentiated at a cortical level according to context), leading to pitfalls in research methodology. If each emotion is not physiologically distinctive, there can be no biological marker for each type or subtype of emotional pathology, and thus most current research in this area would be inappropriate in design. Insofar as “panicogenic” compounds that can experimentally induce anxiety are concerned, it must be remembered that several quite different drugs can provoke panic attacks, and then mainly when anticipatory set has been established in vulnerable subjects (i.e., subjects who have a history of responding to even slight stress or bodily discomfort with severe and disabling anxiety symptoms).

4. Some of the problems of biological psychiatry derive from *general ideological premises* not associated with any particular research methodology. In this venue, there is the fantastic conceit that psychiatric diagnosis, based on a historically evolved descriptive clinical phenomenology, actually coincides with biological parameters that underlie and cause the behavior. van Praag (1993) vehemently warned fellow biological re-searchers that diagnosis in psychiatry is too unclear and unreliable to be a satisfactory correlate in research; instead, he recommended only the investigation of somatic aspects of well-defined symptoms. Moreover, the system of psychiatric classification we now use has been created by generations of brilliant clinicians, as well as the consensus vote of their professional colleagues on the successive DSM committees, but it is a system much too subjective, debatable, and culture-bound to be taken literally as representing biological truth. Dumont (1984) has been eloquent on this point:

Modern medicine has been guilty of what Alfred North Whitehead termed “the fallacy of misplaced concreteness.” Nowhere is this more true than with mental, intellectual, or behavioral disorders. Contemporary psychiatry is going through a paroxysm of line-drawing. It is attempting to divide all human behavior into discrete categories of “illness” decided by a consensus. The schizophrenic label provides the best example of an arbitrary and fluid designation wreaking havoc in its efforts to assume the authority of a “disease.” Schizophrenia is a German invention (it could not have been called a “discovery”). (pp. 327-328)

Unfortunately, the preponderance of research contributed by bio-logical psychiatry up to the present is rendered questionable or even invalidated by the criticisms just presented. A harsh judgment perhaps, but it remains a puzzlement how a field with so many distinguished practitioners could be so susceptible to being thus rebuked. Sad to say, much of the work reviewed in the course of this chapter can be characterized in the same fashion as the evaluation of genetic re-search in schizophrenia by Cassou, Schiff, & Stewart (1980): “Garbage in, garbage out” (p. 124).

A survey of the field of biological psychiatry should not end on such a dour note; there *are* some achievements to applaud. The quality of clinical methodology and inference is improving at last, with the result that recent studies are far more sophisticated. For example, the Kendler et al. Roscommon study (1993a) does not interpret its family history data as showing genetic causation of schizophrenia; instead, it refers more cautiously to some admixture of genetic and environmental causation. The Gordis et al. (1990) review of the alcoholism gene study is a masterpiece of critical acumen. Some researchers now carefully avoid any reductionistic thinking and view somatic mechanisms as mediators, not determinants; indeed, van der Kolk (1988) has suggested that traumatic psychosocial experiences, especially in early life, influence and change neurological functioning. This represents an alternative biological paradigm to the reductionist models that have been so pervasive in psychiatry in the last two decades of the twentieth century.

REFERENCES

- Abood, L. (1960). A chemical approach to the problem of mental disease. In D. Jackson (Ed.), *The etiology of schizophrenia* (pp. 99-119). New York: Basic Books.
- Adler, T. (1990). Alcoholism gene study is controversial. *The American Psychological Association Monitor*, 21, 8.
- Akiskal, H., & McKinney, W. (1975). Overview of depression: Integration of ten conceptual models into a comprehensive clinical frame. *Archives of General Psychiatry*, 32, 285-305.
- Akiskal, H., & Webb, W. (1978). *Psychiatric diagnosis: Exploration of biological predictors*. New York: SP Medical & Scientific Books.
- Angier, N. (1993, January 13). Scientists now say they can't find a gene for manic-depressive illness. *New York Times*, Cl.
- Bader, M. J. (1990). A response to Reginald E. Zelnick. *Tikkun*, 5, 48-50. Bandura, A. (1973). *Aggression: A social learning approach*.

Englewood Cliffs, NJ: Prentice-Hall.

Bassett, A., McGillivray, B., Jones, B., & Pantzar, J. (1988, April 9). Partial trisomy chromosome 5 cosegregating with schizophrenia. *Lancet*, *1*, 799-800.

Bateson, G., Jackson, D., Haley, J., & Weakland, J. (1956). Towards a theory of schizophrenia. *Behavioral Science*, *1*, 251-264.

Benjamin, L. (1976). A reconsideration of the Kety and associates study of genetic factors in the transmission of schizophrenia. *American Journal of Psychiatry*, *133*, 1129-1137.

Bercel, N. (1960). A study of the influence of schizophrenic serum on the behavior of the spider: Zilla-X-Notata. In D. Jackson (Ed.), *The etiology of schizophrenia* (pp. 159-174). New York: Basic Books.

Bignami, G. (1982). Disease models and reductionist thinking in the bio-medical sciences. In S. Rose (Ed.), *Against biological determinism* (pp. 94-110). London: Allison & Busby.

Block, M. (1965). *Alcoholism: Its facets and phases*. New York: John Day.

Blum, K., Noble, E., Sheridan, P., Montgomery, A., Ritchie, T., Jagadeeswaran, P., Nogami, H., Briggs, A., & Cohn, J. (1990). Allelic association of human dopamine D2 receptor gene in alcoholism. *Journal of the American Medical Association*, *263*, 2055-2060.

Borgoankar, D., & Shah, S. (1974). The XYY chromosome male-or syndrome?

Progress in Medical Genetics, *10*, 135-222.

Bowlby, J. (1951). Maternal care and mental health. *Bulletin of the World Health Organization*, *3*, 355-534.

Buchsbaum, M., & Inquar, D. (1982). New visions of the schizophrenic brain: Regional differences in electrophysiology, blood flow, and cerebral glucose use. In F. Henn & H. Nasrallah (Eds.), *Schizophrenia as a brain disease* (pp. 235-252). New York: Oxford University Press.

Cannon, T. D., Mednick, S., Parnas, J., Schulsinger, F., Praestholm, J., & Vestegaard, A. (1993). Developmental brain abnormalities in the offspring of schizophrenic mothers. Part I: Contributions of genetic and perinatal factors. *Archives of General Psychiatry*, *50*, 551-564.

Cannon, W. (1929). *Bodily changes in pain, hunger, fear, and rage: An account of recent researches into the function of emotional excitement*. New York: Appleton.

Carr, D., & Sheehan, D. (1984). Evidence that panic disorder has a metabolic cause. In J. Ballenger (Ed.), *Biology of agoraphobia* (pp. 100-107). Washington, DC: American Psychiatric Press.

Carson, R. C., & Sanislow, C. A. (1993). The schizophrenias. In P. B. Sutker & H. E. Adams (Eds.), *Comprehensive handbook of psychopathology* (pp. 295-298). New York: Plenum.

Cassou, B., Schiff, M., & Stewart, J. (1980). Genetique et schizophrénie: Reevaluation d'un consensus. *Psychiatrie de l'Enfant*, *23*, 87-201.

Chase, A. (1977). *The legacy of Malthus: The new scientific racism*. New York: Knopf.

Clayton, P. (1983). Epidemiologic and risk factors in suicide. *Psychiatric Update*, *2*, 428-434.

Cleaver, E. (1967). *Soul on ice*. New York: McGraw-Hill.

Clinard, M., & Meier, R. (1975). *Sociology of deviant behavior* (5th ed.). New York: Holt, Rinehart & Winston.

Cloninger, C. (1978). The antisocial personality. *Hospital Practice*, *13*, 97-106. Cloninger, C., & Reich, T. (1976). Genetic heterogeneity in alcoholism and sociopathy. In M. Sperber & L. Jarvik (Eds.), *Psychiatry and genetics* (pp. 56-65). New York: Basic Books.

Conrad, P. (1980). On the medicalization of deviance and social control. In D. Ingleby (Ed.), *Critical psychiatry: The politics of mental health* (pp. 102-119). New York: Pantheon.

Costello, C. (1976). *Anxiety and depression: The adaptive emotions*. Montreal: McGill-Queen's University Press.

Cox, W. (1987). Alcoholism: Personality theory and research. In H. Blane & K. Leonard (Eds.), *Psychological theories of drinking and*

alcoholism (pp. 55-89). New York: Guilford Press.

Craike, W., & Slater, E. (1945). *Folie a deux* in uniovular twins reared apart. *Brain*, 68, 213-221.

Crowe, R. (1982). Recent genetic research in schizophrenia. In F. Henn & H. Nasrallah (Eds.), *Schizophrenia as a brain disease* (pp. 235-252). New York: Oxford University Press.

Crowe, R. (1984). The role of genetics in the etiology of panic disorder. *Psychiatric Update*, 3, 402-410.

Dugdale, R. (1887). *The Jukes: A study of crime, pauperism, disease, and heredity*. New York: Putnam.

Dumont, M. P. (1984). The nonspecificity of mental illness. *American Journal of Orthopsychiatry*, 54, 326-334.

Dunham, H. (1977). Schizophrenia: The impact of sociocultural factors. *Hospital Practice*, 12, 61-68.

Eaves, L. J., Eysenck, H.J., & Martin, N. G. (1989). *Genes, culture, and personality: An empirical approach*. London: Academic Press.

Egeland, J., Gerhard, D., Pauls, D., Sussex, J., Kidd, K., Allen, C., Hostetter, A., & Housman, D. (1987). Bipolar affective disorders linked to DNA markers in chromosome 11. *Nature*, 325, 783-787.

Ford, B. D. (1993). Emergenesis: An alternative and a confound. *American Psychologist*, 48, 1294.

Fort, J. (1981). *The addicted society*. New York: Grove.

Fox, R. (1967). Introduction. In R. Maickel (Ed.), *Biochemical factors in alcoholism* (pp. vii-xi). London: Pergamon Press.

Fromm-Reichmann, F. (1959). *Psychoanalysis and psychotherapy*. Chicago: University of Chicago Press.

Gelernter, J., Goldman, D., & Risch, N. (1993). The A1 allele at the D2 dopamine receptor gene and alcoholism. *Journal of the American Medical Association*, 269, 1673-1677.

Gellhorn, E. (1964). Recent investigation of the physiological basis of emotions. In P. Hoch & J. Zubin (Eds.), *Anxiety* (pp. 205-217). New York: Hofner.

Gershon, E. (1983). The genetics of affective disorder. *Psychiatric Update*, 2, 434-457.

Goddard, H. (1912). *The Kallikak family: A study in the heredity of feeble-mindedness*. New York: Macmillan.

Goleman, D. (1990, March 22). Brain structure differences linked to schizophrenia in study of twins. *New York Times*, B15.

Goodwin, D., Schulsinger, F., Hermansen, L., Guze, S., & Winokur, G. (1973). Alcohol problems in adoptees raised apart from alcoholic parents. *Archives of General Psychiatry*, 28, 238-243.

Goodwin, D., Schulsinger, F., Moller, N., Hermansen, L., Winokur, G., & Guze, S. (1974). Drinking problems in adopted and nonadopted sons of alcoholics. *Archives of General Psychiatry*, 30, 164-169.

Gordis, E., Tabakoff, B., Goldman, D., & Berg, K. (1990). Editorials: Finding the gene(s) for alcoholism. *Journal of the American Medical Association*, 263, 2094-2095.

Goring, C. (1913). *The English convict: A statistical study*. London: Darling & Son. Gorman, J. (1984). The biology of anxiety. *Psychiatric Update*, 3, 467-482.

Gottesman, I., & Erlenmeyer-Kimling, L. (1971). Prologue: A foundation for informed eugenics. *Social Biology*, 18 (Suppl.), S1-S8.

Gottesman, I., & Shields, J. (1972). *Schizophrenia and genetics: A twin study vantage point*. New York: Academic Press.

Gottesman, I., & Shields, J. (1982). *Schizophrenia-the epigenetic puzzle*. Cambridge, England: Cambridge University Press.

Gould, S. J. (1981). *The mismeasure of man*. New York: Norton.

Greenspan, S. (1987). *Infants in multi-risk families*. Madison: International Universities Press.

Grosz, H., & Farmer, B. (1972). Pitts and McClure's lactate-anxiety study revisited. *British Journal of Psychiatry*, 120, 415-418.

Guggenheim, F., & Nadelson, C. (1982). *Major psychiatric disorders*. New York: Elsevier.

Hare, R. (1970). *Psychopathy: Theory and research*. New York: Wiley.

- Henig, R. (1988, September 11). Chosen and given. *New York Times Magazine*, 70-72.
- Henry, J. (1971). *Pathways to madness*. New York: Random House.
- Heston, L. (1966). Psychiatric disorders in foster home-reared children of schizophrenic mothers. *British Journal of Psychiatry*, 112, 819-825.
- Heston, L. (1970). The genetics of schizophrenia and schizoid disease. *Science*, 167, 249-256.
- Heston, L., Denney, D., & Pauly, I. (1966). The adult adjustment of persons institutionalized as children. *British Journal of Psychiatry*, 112, 1103-1110.
- Hicks, R., Okonek, A., & Davis, J. (1980). The pharmacologic approach. In I. L. Kutash, L. B. Schlesinger, & Associates (Eds.), *Handbook on stress and anxiety* (pp. 428-450). San Francisco: Jossey-Bass.
- Hodgkinson, S., Sherrington, R., Curling, H., Marchbanks, R., Reeder, S., Mallet, J., McInnis, M., Petursson, H., & Brynjolfsson, J. (1987). Molecular genetic evidence in manic depression. *Nature*, 325, 805-806.
- Hollander, E., Fay, M., Cohen, B., Campeas, R., Gorman, J., & Liebowitz, M. (1988). Serotonergic and noradrenergic sensitivity in obsessive-compulsive disorder: Behavioral findings. *American Journal of Psychiatry*, 145, 1015-1017.
- Hollingshead, A., & Redlich, F. (1958). *Social class and mental illness: A community study*. New York: Wiley.
- Hollister, L. (1968). *Chemical psychoses: LSD and related drugs*. Springfield, IL: Thomas.
- Hutchings, B., & Mednick, S. (1975). Registered criminality in the adoptive and biological parents of registered male criminal adoptees. In R. Fieve, D. Rosenthal, & H. Brill (Eds.), *Genetic research in psychiatry* (pp. 105-116). Baltimore: Johns Hopkins University Press.
- Ingleby, D. (1980). Understanding "mental illness." In D. Ingleby (Ed.), *Critical psychiatry: The politics of mental health* (pp. 23-71). New York: Pantheon.
- Ingleby, D. (1981). The politics of psychology: Review of a decade. *Psychology and Social Theory*, 2, 4-18.
- Izard, C. (1972). *Patterns of emotion: A new analysis of anxiety and depression*. New York: Academic Press.
- Jackson, D. (1960). A critique of the literature on the genetics of schizophrenia. In D. Jackson (Ed.), *The etiology of schizophrenia* (pp. 37-87). New York: Basic Books.
- Jacobs, P., Brunton, M., Melville, M., Brittain, R., & McClelland, W. (1965). Aggressive behavior, mental subnormality, and the XYY male. *Nature*, 208, 1351-1352.
- Jellinek, E. M. (1960). *The disease concept of alcoholism*. New Haven, CT: Hill-house Press.
- Johnson, A., & Szurek, S. (1952). The genesis of antisocial acting out in children and adults. *Psychoanalytic Quarterly*, 21, 323-343.
- Juel-Nielsen, N. (1965). Individual and environment: A psychiatric-psychological investigation of MZ twins reared apart. *Acta Psychiatrica Scandinavica*, 183 (Suppl.), Ad volume 40, 1964, Suppl. 183.
- Kallmann, F. (1938). *The genetics of schizophrenia*. New York: Augustin. Kallmann, F. (1946). The genetic theory of schizophrenia. *American Journal of Psychiatry*, 103, 309-322.
- Kallmann, F., & Roth, B. (1956). Genetic aspects of preadolescent schizophrenia. *American Journal of Psychiatry*, 112, 599-606.
- Kamin, L. (1974). *The science and politics of IQ*. Potomac, MD: Erlbaum. Kendler, K. (1987). Genetics of schizophrenia. *Psychiatric Update*, 6, 25-41.
- Kendler, K., Heath, A., Martin, M., & Evans, L. (1987). Symptoms of anxiety and symptoms of depression: Same genes, different environments? *Archives of General Psychiatry*, 44, 451-457.

- Kendler, K., McGuire, M., Gruenberg, A., O'Hare, E., Spellman, M., & Walsh, D. (1993a). The Roscommon family study. Part I: Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Archives of General Psychiatry*, 50, 527-540.
- Kendler, K., McGuire, M., Gruenberg, A., O'Hare, E., Spellman, M., & Walsh, D. (1993b). The Roscommon family study. Part II: The risk of non-schizophrenic, non-affective psychosis in relatives. *Archives of General Psychiatry*, 50, 645-652.
- Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior Genetics*, 23, 21-27.
- Kennedy, J., Giuffra, N., Moises, H., Cavalli-Sforza, L., Pakstis, A., Kidd, J., Castiglione, C., Sjogren, B., Wetterberg, L., & Kidd, K. (1988). Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. *Nature*, 336, 167-170.
- Kety, S. (1975). Progress toward an understanding of the biological substrates of schizophrenia. In R. Fieve, D. Rosenthal, & H. Brill (Eds.), *Genetic re-search in psychiatry* (pp. 15-26). Baltimore: Johns Hopkins University Press.
- Kety, S. (1979). Disorders of the human brain. *Scientific American*, 241, 202-214.
- Kety, S. (1983). Observations on genetic and environmental influences in the etiology of mental disorder from studies on adoptees and their relatives. In *Genetics of neurological and psychiatric disorders*, (pp. 105-114). [Research Publications: Association for Research in Nervous and Mental Disease, Vol. 60,] New York: Raven Press.
- Kety, S., Rosenthal, D., Wender, P., & Schulsinger, F. (1968). The types and prevalence of mental illness in the biological and adoptive families of schizophrenics. In D. Rosenthal & S. Kety (Eds.), *The transmission of schizophrenia* (pp. 345-362). Oxford, England: Pergamon Press.
- Kevles, D. (1985). *In the name of eugenics*. New York: Knopf.
- Kanner, M. (1982). *The tangled wing: Biological constraints on the human spirit*. New York: Holt, Rinehart & Winston.
- Krimmel, H. (1971). *Alcoholism*. New York: New York Council for Social Work Education.
- Lader, M. (1990). The biology of panic disorder: A long-term view and critique. In J. Walker, G. Norton, & C. A. Ross (Eds.), *Panic disorder and agoraphobia* (pp. 150-174). Pacific Grove, CA: Brooks/Cole.
- Lader, M. (1991). Bio-psycho-social interactions in anxiety and panic disorders: A speculative perspective. *Irish Journal of Psychological Medicine*, 8, 154-159.
- Laing, R. (1972). *The politics of the family*. New York: Vintage Books.
- Lander, E. (1988). News and views: Splitting schizophrenia. *Nature*, 336, 105-106.
- Levinson, H. (1986). *Phobia-free: A medical breakthrough linking ninety percent of all phobias and panic attacks to a hidden physical problem*. New York: Evans.
- Lewontin, R., Rose, S., & Kamin, L. (1984). *Not in our genes: Biology, ideology, and human nature*. New York: Pantheon.
- Lidz, T. (1973). *The origin and treatment of schizophrenic disorders*. New York: Basic Books.
- Lidz, T., & Blatt, S. (1983). Critique of the Danish-American studies of the bio-logical and adaptive relatives of adoptees who became schizophrenic. *American Journal of Psychiatry*, 140, 426-434.
- Lidz, T., Blatt, S., & Cook, B. (1981). Critique of the Danish-American studies of the adopted-away offspring of schizophrenic parents. *American Journal of Psychiatry*, 138, 1063-1068.
- Lipowski, Z. J. (1989). Psychiatry: Mindless or brainless, both or neither? *Canadian Journal of Psychiatry*, 34, 249-254.
- Lipton, M. (1970). The relevance of chemically induced psychoses to schizophrenia. In D. Efron (Ed.), *Psychotomimetic Drugs* (pp. 231-240). New York: Raven Press.
- Liston, E., & Jarvik, L. (1976). Genetics of schizophrenia. In M.A. Sperber & L. Jarvik (Eds.), *Psychiatry and Genetics* (pp. 76-94). New York: Basic Books.
- Livesley, W. J., Jang, K. L., Jackson, D. N., & Vernon, P. A. (1993). Genetic and environmental contributions to dimensions of

personality disorder. *American Journal of Psychiatry*, 150, 1826-1831.

Madsen, W. (1974). *The American alcoholic: The nature-nurture controversy in alcohol research and therapy*. Springfield, IL: Thomas.

Magid, K., & McKelvey, C. (1987). *High risk: Children without a conscience*. Toronto: Bantam Books.

Mandler, G. (1984). *Mind and body*. New York: Norton.

Marmorstein, J., & Marmorstein, N. (1979). *The psychometabolic blues*. Santa Barbara, CA: Woodbridge Press.

McClelland, D., Davis, W., Kalin, R., & Wanner, E. (1972). *The drinking man: A theory of human motivation*. New York: Free Press.

McCord, W., & McCord, J. (1960). *Origins of alcoholism*. Stanford, CA: Stanford University Press.

Mednick, S. (1970). Breakdown in individuals at high risk for schizophrenia: Possible predispositional perinatal factors. *Mental Hygiene*, 54, 50-63.

Mednick, S., Gabrielli, W., & Hutchings, B. (1984). Genetic influences in criminal convictions: Evidence from an adoption cohort. *Science*, 224, 891-894.

Meehl, P. (1972). A critical afterword. In I. Gottesman & J. Shields (Eds.), *Schizophrenia and genetics: A twin study vantage point* (pp. 367-415). New York: Academic Press.

Mendelson, J., & Mello, N. (1979). Biologic concomitants of alcoholism. *New England Journal of Medicine*, 301, 912-921.

Mendlewicz, J., & Rainer, J. (1977). Adoption study supporting genetic transmission in manic-depressive illness. *Nature*, 268, 327-329.

Morris-Yates, A., Andrews, G., Howie, P., & Henderson, S. (1990). Twins: A test of the equal environments assumption. *Acta Psychiatrica Scandinavica*, 81, 322-326.

Munkvad, I., Fog, R., & Randrup, A. (1975). Amphetamine psychosis: A useful model of schizophrenia? In H. van Praag (Ed.), *On the origin of the schizophrenic psychoses* (pp. 50-57). Amsterdam: De Erven Bohn DV.

Neale, J., & Oltmanns, T. (1980). *Schizophrenia*. New York: Wiley.

Newman, H., Freeman, F., & Holzinger, K. (1937). *Twins: A study of heredity and environment*. Chicago: University of Chicago Press.

Orne, M. (1962). On the social psychology of the psychological experiment.

American Psychologist, 17, 776-783.

Paul, S., & Skolnick, P. (1984). The biochemistry of anxiety: From pharmacotherapy to pathophysiology. *Psychiatric Update*, 3, 482-490.

Peele, S. (1990, August). Second thoughts about a gene for alcoholism. *The Atlantic Monthly*, 52-58.

Pittman, D., & Gordon, C. (1958). *The revolving door*. New York: Free Press.

Pitts, F., & McClure, J. (1967). Lactate metabolism in anxiety neurosis. *New England Journal of Medicine*, 277, 1329-1336.

Plomin, R., Corley, R., Defries, J.C., & Fulker, D. W. (1990). Individual differences in television viewing in early childhood: Nature as well as nurture. *Psychological Science*, 1, 371-377.

Plomin, R., Defries, J.C., & McClearn, G. K. (1980). *Behavior genetics: A primer*.

San Francisco: Freeman.

Plutchik, R. (1962). *The emotions: Facts, theory, and a new model*. New York: Random House.

Rainer, J. (1976). Genetics of neurosis and personality disorder. In M. Sperber &

L. Jarvik (Eds.), *Psychiatry and genetics* (pp. 56-65). New York: Basic Books. Robertson, M. (1987). News and views: Molecular genetics of the mind. *Nature*, 325, 755.

Rosenthal, D. (1970). *Genetic theory and abnormal behavior*. New York: McGraw-Hill.

- Rosenthal, D. (1971). *Genetics of psychopathology*. New York: McGraw-Hill.
- Rosenthal, D., Wender, P., Kety, S., Schulsinger, F., Welner, J., & Ostegaard, L. (1968). Schizophrenics' offspring reared in adoptive homes. In D. Rosenthal & S. Kety (Eds.), *The transmission of schizophrenia* (pp. 377-391). Oxford, England: Pergamon Press.
- Rosenthal, D., Wender, P., Kety, S., Welner, J., & Schulsinger, F. (1971). The adopted-away offspring of schizophrenics. *American Journal of Psychiatry*, 128, 307-311.
- Ross, C. A. (1986). Biological tests for mental illness - their use and misuse. *Biological Psychiatry*, 21, 431-435.
- Roy-Byrne, P., & Cowley, D. (1988). Panic disorder: Biological aspects. *Psychiatric Annals*, 18, 457-463.
- Rutstein, D., & Veech, R. (1978). Genetics and addiction to alcohol. *New England Journal of Medicine*, 298, 1140-1141.
- Sacks, O. (1985). *The man who mistook his wife for a hat and other clinical tales*. London: Duckworth.
- Scarr, S., & Carter-Saltzman, L. (1979). Twin method: Defense of a critical assumption. *Behavior Genetics*, 9, 527-542.
- Schachter, S., & Singer, J. E. (1962). Cognitive, social, and physiological determinants of emotional state. *Psychological Review*, 69, 379-399.
- Scheinfeld, A. (1939). *You and heredity*. New York: Frederick Stokes.
- Schildkraut, J., Schatzberg, A., Mooney, J., & Orsulak, P. (1983). Depressive disorders and the emerging field of psychiatric chemistry. *Psychiatric Update*, 2, 457-471.
- Schmeck, H. (1989, November 7). Scientists now doubt they found faulty gene linked to mental illness. *New York Times*, Science Section, C3.
- Schuckit, M. (1984). Genetic and biochemical factors in the etiology of alcoholism. *Psychiatric Update*, 3, 320-328.
- Schuckit, M., Goodwin, D., & Winokur, G. (1972). A study of alcoholism in half-siblings. *American Journal of Psychiatry*, 128, 1131-1136.
- Schuckit, M., & Raynes, V. (1979). Ethanol ingestion: Differences in blood acetaldehyde concentration in relatives of alcoholics and controls. *Science*, 203, 54-55.
- Schulsinger, F., Kety, S., Rosenthal, D., & Wender, P. (1979). A family study of suicide. In M. Schou & E. Stromgren (Eds.), *Origin, prevention, and treatment of affective disorders* (pp. 277-287). London: Academic Press.
- Schultz, R. I. (1965). *Sensory restriction: Its effects on behavior*. New York: Academic Press.
- Scott, K. G., & Carran, D. T. (1987). The epidemiology and prevention of mental retardation. *American Psychologist*, 42, 801-804.
- Sheehan, D. (1982). Panic attacks and phobias. *New England Journal of Medicine*, 307, 156-158.
- Sheldon, W. (1940). *The varieties of human physique: An introduction to constitutional psychology*. New York: Harper & Brothers.
- Sherrington, R., Brynjolfsson, J., Petursson, H., Potter, M., Duddleston, K., Barraclough, B., Wasmuth, J., Dobbs, M., & Curling, H. (1988). Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, 336, 164-167.
- Shields, J. (1962). *MZ twins brought up apart and brought up together*. London: Oxford University Press.
- Slater, E. (1961). Hysteria 311. *The Journal of Mental Science*, 107, 359-371.
- Slater, E. (1968). A review of earlier evidence on genetic factors in schizophrenia. In D. Rosenthal & S. Kety (Eds.), *The transmission of schizophrenia* (pp. 15-26). Oxford, England: Pergamon Press.
- Smith, J. D. (1985). *Minds made feeble: The myth and legacy of the Kallikaks*. Rockville, MD: Aspen Publications.
- Smythies, J., Coppen, A., & Kreitman, N. (1968). *Biological psychiatry: A review of recent advances*. New York: Springer Verlag.
- Snyder, S. (1976, May 17). *Medical World News*, 24.
- Snyder, S. (1977). Biochemical factors in schizophrenia. *Hospital Practice*, 12, 133-140.
- Sobel, D. (1961). Children of schizophrenic parents: Preliminary observations on early development. *American Journal of Psychiatry*, 118, 512-517.

- Sherlin, H. (1974). *Separating parents and adolescents: A perspective on running away, schizophrenia and waywardness*. New York: Quadrangle.
- Suddath, R., Christison, G., Torrey, E. F., Casanova, M., & Weinberger, D. (1990). Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, 332, 789-794.
- Thio, A. (1978). *Deviant behavior*. New York: Harper & Row.
- Tienari, P. (1991). Interaction between genetic vulnerability and family environment: the Finnish adoptive study of schizophrenia. *Acta Psychiatrica Scandinavica*, 84, 460-465.
- Tolstoy, L. (1946). *Resurrection* (R. Edmonds, Trans.) London: Penguin Books. (Original work published 1899)
- Torgersen, S. (1983). Genetic factors in anxiety disorders. *Archives of General Psychiatry*, 40, 1085-1089.
- Torrey, E. F. (1983). *Surviving schizophrenia: A family manual*. New York: Harper & Row.
- Trice, H. (1966). *Alcoholism in America*. New York: McGraw-Hill.
- Tuma, A., & Masser, J. (1975). *Anxiety and the anxiety disorders*. Hillsdale, NJ: Erlbaum.
- van der Kolk, B. A. (1988). The trauma spectrum: The interaction of biological and social events in the genesis of the trauma response. *Journal of Traumatic Stress*, 1, 273-290.
- van Praag, H. M. (1977). The significance of dopamine for the mode of action of neuroleptics and the pathogenesis of schizophrenia. *British Journal of Psychiatry*, 130, 463-474.
- van Praag, H. M. (1993). *"Make-believes" in psychiatry, or the perils of progress*. New York: Brunner /Mazel.
- van Praag, H. M., & Korf, J. (1975). The dopamine hypothesis: Some direct observations. In H. van Praag (Ed.), *On the origin of the schizophrenic psychoses* (pp. 81-98). Amsterdam: De Erven Bohn BV.
- Wallace, M. (1986). *The silent twins*. New York: Ballantine.
- Wender, P. (1976, May 17). *Medical World News*, 23.
- Wender, P., & Klein, D. (1981, February). The promise of biological psychiatry. *Psychology Today*, 25-41.
- Wender, P., Rosenthal, D., Kety, S., Schulsinger, F., & Welner, J. (1974). Cross-fostering: A research strategy for clarifying the role of genetic and experiential factors in the etiology of schizophrenia. *Archives of General Psychiatry*, 30, 121-128.
- Wilson, J., & Herrnstein, R. (1985). *Crimes and human nature*. New York: Simon & Schuster.
- Zerbin-Rudin, E. (1972). Genetic research and the theory of schizophrenia. *International Journal of Mental Health*, 1, 42-62.

Research Open

Errors Of Logic In Biological Psychiatry

Colin A. Ross

When I entered my psychiatry residency, I believed that research had demonstrated the genetic foundation of schizophrenia and had shown that schizophrenia is primarily a biomedical brain disease. This view was almost universally accepted at my medical school, and I never heard serious criticism of it while in training. It was by a gradual process that I began to become more and more aware of the cognitive errors pervading clinical psychiatry - unwittingly demonstrated to me by my residency supervisors. As I became more acquainted with the psychiatric literature, I learned that these cognitive errors are ubiquitous in the profession and are rarely challenged.

I also observed that challenging either of the dominant paradigms in psychiatry - psychoanalysis and biomedical reductionism - could lead to a charge of "antipsychiatry," and I was surprised at the ease with which the complex ideas of Thomas Szasz (1974) were casually dismissed as antipsychiatry, as if they did not demand careful and reasoned refutation. When I read Szasz myself, I was not convinced at all by his thesis that schizophrenia is a myth of psychiatric construction, and I still am not, but much of his writing is civil-libertarian, psychological in nature, and no different from the accepted wisdom of my supervisors who called him an anti-psychiatrist.

In the first year of my residency, I listened carefully to staff psychiatrists who made discontinuous switches back and forth between the two dominant paradigms in discussion of a single case, within the same spoken paragraph, and I realized that psychiatry does not have a coherent, unified model or doctrine. In one instance, a psychiatrist was discussing a young man with schizophrenia from a biomedical case management point of view. Suddenly, he lurched into a discussion of projection as the underlying mechanism for some of the man's symptoms; then, after a couple of sentences, he as suddenly returned to his biomedical mode and vocabulary. Although this might be heralded as an eclectic approach, it was simply unintegrated. Psychiatry suffers from an identity disorder, which it is currently trying to solve by forcing the adoption of a bioreductionist paradigm.

I was taught that psychiatry has become much more modern and scientific since the introduction of neuroleptics in the 1950s, and the enthusiasm of psychiatrists for biological explanations of mental illness was presented as being based on a solid scientific foundation. It was therefore somewhat surprising to notice in the *Comprehensive Textbook of Psychiatry/III* (Kaplan, Freedman, & Sadock, 1980) that in a meta-analysis of double-blind chlorpromazine studies in schizophrenia, the drug was found to be superior to placebo in 55 trials but equal to placebo in 11 (p. 2258). This meant that in 17% of trials, chlorpromazine is no better than placebo in treatment of schizophrenia.

Additionally, a graph on page 2259 showed schizophrenics treated with placebo differing from those treated with chlorpromazine by only one point on a seven-point scale of severity of illness at the end of a large study. Although this was statistically significant, it appeared that the clinical efficacy of chlorpromazine in schizophrenia was far less than the confident, dogmatic statements I was hearing from my supervisors. I did not hear any serious discussion of the possibility that the overall cost-benefit of neuroleptics in schizophrenia may be only modestly positive, although the data in the major textbook pointed directly to this possibility.

I also saw how badly biological psychiatrists want to be regarded as doctors, and accepted by the rest of the medical profession. In their de-sire to be accepted as real clinical scientists, these psychiatrists were building far too dogmatic an edifice on a very meager scientific foundation, and in fact were undermining the scientific basis of psychiatry by pushing their certainty far beyond what the data could support. A chief example of this process was the enthusiasm for the use of the dexamethasone suppression test (DST) as a routine clinical diagnostic test for depression, which peaked during my residency years (1981 to 1985).

Another observation forced on me early in my residency was the universal disavowal of biomedical reductionism upon direct challenge. It was almost as if there was an unconscious program of plausible denial in place. Any direct challenge to the cognitive errors of biomedical reductionism was always met with the response that the biopsychosocial model was accepted throughout biological psychiatry. Once lip service was paid to the biopsychosocial approach, however, and the challenge forgotten, the logical fallacies rose to the conversational surface immediately.

One of the most disturbing effects of the errors of logic in biological psychiatry I witnessed in ten years as a resident and academic psychiatrist, from 1981 to 1991, was their influence on medical students. Already intensively socialized into biomedical reductionism by

the time they arrived on the psychiatry wards, many medical students accepted the folklore and logical errors of biological psychiatry as scientific fact. I would hear them parroting the teaching that psychiatry has become more scientific recently, has many effective drugs, has demonstrated the genetic foundation of schizophrenia, and is moving ever-forward into more specific psychopharmacology. The problem was not that all these propositions were completely false; rather, it was the uncritical acceptance of the dogma that alarmed me.

It was not surprising that medical students accepted the dogma of biomedical reductionism in psychiatry uncritically: they had no time to read and analyze the original literature. What took me a while to understand, as I moved through my residency, was that psychiatrists rarely do the critical reading either. The dogma that the genetic foundation of schizophrenia has been scientifically established is by and large accepted without serious question in contemporary psychiatry, although, as Dr. Pam has shown irrefutably in Chapter 1, the data are sub-scientific in standard.

In this chapter, I discuss errors of logic in biological psychiatry. The errors overlap and intertwine with each other, and some are included for purposes of exposition, when they could be treated as variants of other errors without being listed separately. I do not provide herein references illustrating each error because (a) that is, in part, my task in the next chapter, and (b) finding isolated examples of each error in the literature would not establish the pervasive, tacit nature of the errors, which are similar to the automatic negative thoughts analyzed in cognitive therapy (Beck, Rush, Shaw, & Emery, 1979). The errors are not listed in any particular order; they are interrelated in a complex net, although some are stated explicitly more often than others.

On direct challenge, a biomedical reductionist psychiatrist will disavow adherence to the errors, describe them as oversimplifications or stereotypes, and emphasize that all biological psychiatrists recognize the importance of psychosocial factors in mental illness. This is actually true of some biological psychiatrists, especially the most creative ones, but many are, in fact, pure reductionists in a way that pervades their bedside manner, clinical practice, time management, treatment modalities, diagnostic habits, and even their dress (only bioreductionist psychiatrists wear white lab coats). None of this would necessarily be objectionable if the psychiatrists were internists of the brain; but they aren't, because psychiatry has not acquired even a tiny fraction of the scientific foundation of internal medicine.

It is self-evident that there must be a biological component to mental illness, because without brains patients could not produce symptoms or behaviors, and there could be no psychiatry. There is nothing anti-biological about my analysis of these cognitive errors.

If It Runs In Families, It Must Be Genetic

During the third year of my residency, I spent a year on a teaching fellowship devising the first scientifically reliable method of teaching and evaluating biopsychosocial psychiatric case formulations (Ross & Leichner, 1986; Ross, Leichner, Matas, & Anderson, 1990). At this stage in my career, I was still uncritically accepting the dictum that a family history of a given psychiatric disorder is evidence of a genetic component to the illness. I taught residents and students to make such statements in listing biological factors in their cases, and these declarations of biological etiology were accepted without criticism every time they were made - by myself and all other members of the department. This is how pervasive the logical error was, and still is, in much psychiatric practice.

Scientifically, a pattern of family transmission is neutral with respect to genetic versus environmental etiology. The fact that other family members have been depressed, schizophrenic, alcoholic, or bulimic, does not to the smallest degree support the conclusion that there is a genetic component to the illness. In a psychiatry dominated by dogmatic environmentalism, one hostile to biology, the existence of relatives with the same diagnosis would be uncritically accepted as convincing evidence that the disorder was *learned*.

This central dogma in biological psychiatry is adhered to solely because of ideology, an intellectual distortion that can occur only when there is a pervasive suspension of critical, scientific thinking. Scientifically, the only conclusion that can be reached from studying the pattern of occurrence of a disorder in a pedigree is an inversion of biological psychiatry's logical error: *If there is no familial pattern, one can rule out an inherited cause*. If there is a pattern of family transmission, on the other hand, there may be a purely inherited cause, a purely environmental cause, or a mixture of the two.

A simple example will illustrate the point. Let's assume that, going back for four generations, every single member of a pedigree who had schizophrenia also had a characteristic abnormality of the fingernails, and no non-schizophrenics had the nail abnormality. According to the logical error of bioreductionist psychiatry, the nail abnormality would be regarded as a marker for schizophrenia, and someone would search the nail physiology literature for information about the role of peripheral dopamine in nail physiology. This would seem reasonable, but it is not. The error of the bioreductionist is the degree of dogmatic certainty that a genetic conclusion can be reached and that the nail abnormality is linked to the schizophrenia. The certainty results in decisions about what kind of research gets funded, who gets full professorship, and how psychiatry is marketed to politicians and insurance companies. I have deliberately

chosen a fingernail abnormality as an example because the link between the fingernails and schizophrenia is not intuitively obvious, and therefore the fallacy in the thinking is more apparent. However, the same logic applies when the abnormality is in the brain, or on a specific chromosome: within biological psychiatry, a dogmatic jump to a high level of certainty of direct etiological linkage is made, at both genetic and pathophysiological levels, and the new finding is prematurely heralded as a breakthrough and as further proof of the biological nature of schizophrenia. In the pedigree in question, it may be that cultural factors result in schizophrenics varying their diets in a specific fashion that affects nail growth, and it may be that schizophrenic-pedigree children adopted out of this culture at birth never display the nail abnormality, while those adopted in do. The pattern of transmission of schizophrenia and fingernail abnormalities could get heralded as further proof of the anthropologically determined nature of schizophrenia in a psychiatry dominated by a different ideology.

Consider another pedigree in which a characteristic eyefold co-occurs with speaking Chinese. Would we conclude that speaking Chinese is genetically determined and that the eyefold gene is closely linked to the gene for speaking Chinese? That conclusion is preposterous. But the logic is no different from that of biomedical psychiatry, except that biological psychiatrists talk about mental disorders and abnormalities in the brain.

When I was teaching formulation, it was obvious to all that very few specific biological factors could ever be identified in psychiatric cases, other than the fallacious family pedigree argument. In fact, in hundreds of cases formulated and discussed, the only specific biological factor ever identified was discontinuing medications against medical advice, the paradox being that this was a *behavior*, and would be understood in purely nonbiological terms by many psychologists and social scientists. Even here, there was not an exclusive biological factor. At the present time, there is no proof that biology causes schizophrenia, bipolar mood disorder, or any other functional mental disorder.

If It Responds To Medication, It Must Have A Biological Cause

I have heard this cognitive error-and its variants countless times. The chief variant is the belief that clinical response to medications can be used as a factor in the differential diagnosis of psychiatric disorders. As a coeditor of a textbook on panic disorder (Walker, Norton, & Ross, 1991), I consider myself fairly up-to-date on the subject, so I will use it as an example without further referencing.

The phenomenology of panic attacks is well documented, and there are a number of reliable measures for recording and describing them. A classical pattern of clear panic disorder is unmistakable, can be diagnosed with a high degree of interrater reliability (kappa above 0.90), and has major treatment validity in terms of specific response to specific treatments. What do we know about the biopsychosocial matrix of panic disorder?

A classical panic attack in someone with a specific phobia can be set off by a specific environmental trigger such as an elevator, but this same trigger will have no effect on someone without the phobic panic attack. I am referring to someone with panic disorder who has both spontaneous and situational panic attacks, not to someone with a pure simple phobia. We also know that the panic attacks can be triggered in the laboratory by a variety of biological challenges including caffeine, carbon dioxide, sodium lactate, and other agents, while individuals without panic disorder almost always have unremarkable reactions. This observation is placebo-controlled. The phenomenology of psychologically and biologically triggered panic attacks is indistinguishable, except perhaps for a few fine points at most.

Both environmentally cued and biologically induced panic attacks can be blocked by drugs like imipramine, which are effective in the treatment of panic disorder. Panic disorder can also be effectively treated by cognitive-behavioral therapy. The only remaining cell in this matrix is the ability of cognitive-behavioral therapy to block the panic response to biological challenges in individuals with panic disorder. If we assume for the moment and for the purpose of the argument that this is a scientific reality, although the data on this point are not yet conclusive, what can we conclude?

We know that panic disorder tends to run in families and is a strong candidate for the first cognitive error discussed above. We also know that panic attacks can be induced and blocked in all possible combinations at biological and psychosocial levels. Therefore, we cannot conclude that the responsiveness of panic disorder to imipramine and alprazolam is evidence that it must have a biological cause, because other data of equally good quality would support a psychosocial cause. It is a logical fallacy to conclude that treatment response at one level of organization within the organism implies primary causation at that level.

In a biopsychosocial model of panic disorder, one could postulate an inherited predisposition to autonomic hyperarousal, although this could equally as well be environmentally induced by family transactional patterns and cognitive errors. Setting aside whether

the hyperarousal is inherited or culturally induced, we can postulate the existence of such hyperarousal. For panic attacks to occur, characteristic psychodynamics, catastrophizing cognitive errors, and errors in learning need to be present. It is therefore possible to intervene by prescribing drugs that dampen down the arousal to a subthreshold level at which the cognitions cannot trigger panic, or to treat the cognitive errors such that the sub-clinical autonomic instability is of no clinical consequence.

Whether the putative biological abnormality in panic disorder is inherited or not cannot be inferred from any of the above findings or reasoning, yet dogmatic statements that panic disorder is an inherited biomedical brain disease localized in the locus coeruleus can be found within biological psychiatry. This is a locus of control error.

The same logic applies to all medications prescribed for all psychiatric disorders. Panic disorder is a more compelling example than schizophrenia because most cells of the matrix have been filled by data for panic disorder, whereas the situation with schizophrenia is much more muddled.

I have heard many times that response to medication can also be used in differential diagnosis within psychiatry. The pseudomedical nature of this belief is evident if one makes a comparison to internal medicine. An infectious disease may respond with initial symptom suppression to rehydration, steroids, aspirin, or antibiotics, but no internist draws etiological conclusions from these observations or uses the drug response in differential diagnosis. Within psychiatry, such observations are used to support preconceived biomedical reductionist ideology in a way that occurs far less often in other areas of medicine. It is as if the psychiatrists are trying so hard to be doctors that they are overshooting the mark.

Many times, I have heard that a patient's response to lithium, anti-depressants, or neuroleptics can be used in differential diagnosis of bipolar mood disorder versus schizoaffective disorder, versus schizophrenia. Although there is some informal, rough truth to this proposition at the level of an individual patient, the diagnostic conclusions are reached with a far greater degree of certainty than is scientifically warranted. Problems glossed over in reaching such conclusions include the substantial placebo-responsiveness of all three conditions in double-blind trials, the differential-diagnostic nonspecificity of many psychotic symptoms targeted by neuroleptics, the nonspecific actions of neuroleptics such as anxiolysis and behavioral calming, and the impossibility of differentiating pure mood disorder from schizoaffective disorder by lithium response. This impossibility arises from the same logical problems with false positives and negatives as apply to the diagnostic use of the dexamethasone suppression test, to be discussed below. In actual clinical practice, in biological psychiatry, what often occurs is a forcing of diagnosis prior to a trial of medication. I observed this repeatedly, and I mention it although it is not strictly a cognitive error. If a given patient has not responded to lithium, the psychiatrist may begin to selectively ignore symptoms that support a diagnosis of bipolar mood disorder, and give augmented weight to symptoms supporting schizophrenia, prior to initiating a trial of a neuroleptic (in actual practice, this process more often occurs in the reverse direction). In another case, or at another time in the same patient, the weighting of symptoms may go in reverse or there may be a shift toward a trial of an anticonvulsant based on sudden observation of symptoms suggestive of temporal lobe epilepsy, which are usually actually dissociative symptoms.

Concurrent with an increase in the degree of confidence in the pseudoscientific conclusion that the genetic basis of mental disorders has been demonstrated, a paradoxical observation within psychopharmacology is also being made regarding the efficacy of certain medications in a wide variety of different disorders. For instance, serotonin reuptake blockers like fluoxetine can be effective in depression, bulimia, obsessive-compulsive disorder, posttraumatic stress disorder, and other conditions that are supposed to be unrelated to each other.

Alprazolam, first developed as an anxiolytic, is effective in panic disorder and generalized anxiety disorder, but may have antidepressant properties; imipramine, first developed as an antidepressant, is effective in panic disorder. How has biological psychiatry reacted to this development?

One conclusion biological psychiatrists could draw from the fact that one medication works for many different disorders is that there is no biological specificity to different psychiatric disorders. Because this threatens the one gene-one illness model of biomedical reductionism, that conclusion is disallowed (the same logic holds no matter how many risk genes there are). What inference is made in its place? There are several strategies, the first of which is simply not to address the problem, and to keep searching for specific genes for specific illnesses while psychopharmacological research further demonstrates the biological non-specificity of psychiatric disorders. This allows both the genetic research and the drug company contracts to remain in place.

The second strategy is to argue that the disorders responding to a given medication are all variants of a single disorder, usually

depression. This occurred for bulimia, in which the response of bulimia to imipramine was used to argue that bulimia was a variant of depression. This argument was purely artifactual: it depended on the historical accident that imipramine was first shown to be effective for depression, and therefore was classified as an antidepressant. If it had first been shown to be effective for panic disorder and its antidepressant properties had not yet been discovered, then the argument would have to be that bulimia is a variant of panic disorder (perhaps bulimics self-medicate with food to prevent panic attacks, someone would suggest).

The depressive-spectrum argument can only be pushed so far before it threatens the genetic specificity of psychiatric disorders, and the one gene-one illness model can only be softened so far to accommodate the pharmacological data before it collapses. Complicated but nevertheless pseudoscientific efforts to salvage the genetic hypothesis with polygenetic loci, partial penetrance, and other genetic mechanisms will eventually undo themselves because they will lead to a conclusion that one can speak at most of a polygenetic predisposition to psychopathology in general. If there is no specific relationship between the mechanism of action of many effective drugs and diagnostic category, then the only way to maintain the genetic hypothesis would be to dismantle and entirely reorganize the DSM-IV diagnostic system, eliminating the concept of separate categories of mental illness. This would feed back on the genetic hypothesis to undermine its specificity, because there would be no specific clinical disorders if the system was based on family studies, drug responses, and genetic findings alone, rather than on clinical symptoms. There would be no separate mental disorders and no separate genes to find in nature. This reorganization will never happen politically; besides, there is psychotherapeutic treatment outcome specificity to many of the separate diagnostic categories, which will block their unification. The specificity of distinct psychotherapies for different mental disorders could prove to be more rooted in the differential biology of the disorders than the comparatively nonspecific response to medications.

Biological psychiatry has trapped itself in a logic box that will self-destruct.

Proving A Mental Illness Is Biological Will Reduce The Stigma

One of the humanitarian cognitive errors of biological psychiatry is the belief that establishing the genetic and/or biological nature of mental illness will reduce the stigma of psychiatric disorders. This is false reasoning, both politically and logically. Leprosy is a biological illness, but understanding its infectious etiology has done nothing to reduce the stigma of the disorder. Some parents restrict their children from playing with other children who have cancer because they fear infection of their children. These parents demonstrate that establishing the biological nature of a condition does not necessarily reduce stigma, nor does it necessarily result in more informed responses and attitudes.

The reasoning is politically false for several reasons in addition to those just listed. One hope is that a biomedical definition of psychiatric disorders will increase the lobbying power of psychiatry, the effectiveness of consumer lobbies, and the funding of psychiatric treatment and research by making psychiatry more of an equal partner in medicine. To achieve this goal, biological psychiatry goes overboard in emphasizing the biogenetic model, beyond the level observable in the rest of medicine. Cardiovascular disease is not talked about within internal medicine the way biological psychiatrists talk about the gene or genes for schizophrenia, for instance. Of the risk factors for coronary artery disease, a family history is only one; the others are predominately psychosocial in nature - smoking, inadequate exercise, low-nutrition diet, failure to control cholesterol, obesity, and hypertension. Hypertension is almost always idiosyncratic with no defined etiology, and the risk it contributes for coronary artery disease is substantially due to medication noncompliance and failure to modify lifestyle. Coronary artery disease is universally understood within medicine as the final common pathway of many different combinations of factors, with genetics accounting for a small proportion of the variance in the overall population. Pedigrees with specific biomedical risk factors like hyper-lipidoses are a small subset of the general population's morbidity and mortality, yet biological psychiatry behaves as if most or all cases of schizophrenia, by analogy, are due to genetically specific lipid metabolism disorders.

The financial and political success of the cardiovascular lobby depends to a very small degree on the endogenous genetic foundation of such illness, therefore one might conclude that emphasizing the psychosocial and public health factors in major mental illness would be a better political strategy. Similar logic applies to cancer and AIDS re-search, in which environmental variables are key to all public health efforts and preventive measures.

One cannot speak of a gene for lung cancer as such, given the data on smoking, because there would be no clinical cancer in many individuals if they had not smoked heavily for years. One can speak of a set of genes for the oncogenic reaction to cigarette smoke in such individuals, but there is no gene for the disease as such. There is a location in the human genome controlling the interaction of the organism with the cigarette smoke, undoubtedly, but a complex sequence of promoters and cofactors is required to create the

clinical illness. Scientifically, it is necessary to talk about multifactorial etiologies even at the genetic level, none of which by itself can be regarded as a “gene for lung cancer.” Although I am out of my league on the genetic details here, the point I am making is that the discussion of genetics within biological psychiatry is often simplistic and ideologically driven in a way that doesn’t occur elsewhere in medicine to the same degree.

The biogenetic model dominating psychiatry today is too much like that for Huntington’s chorea, or Tay-Sachs disease, which have well-established modes of inheritance. The hope is that schizophrenia can be shown to be another Huntington’s chorea. Within medicine, though, from a public health point of view, such Mendelian illnesses account for a tiny proportion of the severe morbidity and mortality in the general population, and a tiny proportion of the total clinical time of all physicians. The behavior of biological psychiatrists is too often a caricature of the medical approach to serious human illness, driven by reductionist ideology, and fostered by a paucity of serious scientific thinking.

Alcoholism Is A Disease

This doctrine has been adopted throughout the chemical dependency field including Alcoholics Anonymous (AA), despite the fact that it has no scientific foundation and is logically incorrect. The search for the gene for alcoholism is heavily funded currently, and the cognitive error that if it runs in families, it must be genetic, is strongly adhered to in the alcoholism field. This is also true of the cognitive error that a genetic etiology will reduce stigma, because this error has had its most profound influence in the alcoholism field. The idea that alcoholism is inherited is viewed as a scientific fact at many levels in our society, not just within biological psychiatry. The idea that alcoholism is genetic is the leading example of the effective marketing of pseudoscience by biological psychiatry.

There is a paradox here, as in previously analyzed errors of logic: AA workers and biological psychiatrists who view alcoholism as an inherited medical condition simultaneously promulgate the doctrine that the alcoholic has to *decide* to recover before any serious attempt at recovery is possible. Alcoholics who continue to drink heavily are viewed as not yet having made the *choice* to recover, and the inefficacy of treatment efforts is attributed to lack of willpower, personal fiber, and surrender to a higher power on the part of the alcoholic, with no attribution of causality to the model or the treatment method. The alcoholism field is dominated by a tautology in which treatment failure is due to not working the steps hard enough, a conclusion that rules out the possibility of lack of efficacy of the treatment package in subpopulations.

There cannot be a gene for alcoholism, and alcoholism cannot be a biomedical illness, for logical reasons; therefore, no empirical study of the question is required, and the search for the gene can be abandoned. Scarce research funds can be much better utilized elsewhere. Why is this true? I will analyze the simplest form of the model, because the same logic applies to all genetic models of alcoholism, no matter how sophisticated or polygenetic. I will postulate the existence of a single gene for alcoholism, then demonstrate the logical self-contradictions and fallacies inherent in the hypothesis.

One statement that is made about the biological foundations of alcoholism is that alcoholics are born with a reduced tolerance to alcohol, and therefore get drunk more easily than non-alcoholics, resulting in their drinking to intoxication more readily and more often. This concept has been applied in a racist way to findings that Native Americans have different levels of alcohol dehydrogenase than other people, although none of the findings, to my knowledge, has controlled for numerous other factors including lifetime total alcohol dose. The idea that those who get drunk more easily have a *disease* called alcoholism, which places them in a separate category from those who do not have the disease, is untenable for several reasons. For one thing, as the disease progresses, tolerance rises, which should initiate a feedback loop limiting the development of alcoholism, according to sensitivity models, because the alcoholic’s sensitivity becomes less than that of non-alcoholics.

To use alcohol dehydrogenase levels as an example of sensitivity models, this biological variable is distributed in a continuous fashion in the general population, with a range of normal, not in discrete categories. This is a completely different picture from that which occurs in Lesch-Nyan syndrome, a biologically specific inherited deficiency of hypoxanthine, guanine-phosphoribosyl transferase, or other truly genetic enzymatic abnormalities that produce specific clinical syndromes. Alcohol consumption is also distributed in a continuous fashion in the general population, with no valid scientific threshold for case definition, although severe alcoholics can easily be differentiated from teetotalers. This is completely different from Lesch-Nyan syndrome, which one either has or does not have: there is no continuous distribution. In alcoholism, there are many grey-zone cases in which it is a matter of judgment whether the individual is an alcoholic or just someone who likes to drink more than average. This never occurs in truly Mendelian diseases. The fact that specific genetic disorders like Huntington’s chorea may be difficult to diagnose in their early stages is irrelevant to this analysis, as are arguments about partial penetrance.

All theories about differential enzyme levels, or inherited biological sensitivity levels, are scientifically erroneous for another reason: they are basically dose-response curve models in which a shift in the curve defines the presence of the illness. This is fallacious because the shift of the curve occurs in a continuous fashion within a normal range, as stated above. A more important fallacy is the fact that the only effect of the curve shift is to reduce the number of drinks required to get drunk. This could be a significant factor in the development of alcoholism only if many people failed to experience full expression of their alcoholic gene due to financial or time constraints, which is a necessary postulate of the model. Anyone who has been to a pub or bar should understand the absurdity of this concept.

To scientifically demonstrate the reality of a dose-response model, one would have to demonstrate that a significant number of non-alcoholics will become clinical alcoholics if they earn more or have more time to spend in bars getting drunk. Otherwise, differential enzyme levels in alcoholics are of no relevance to development of the disorder of alcoholism. What defines the alcoholic must be another factor having to do with experiencing intoxication as reinforcing, pleasant, and a reward. It is more accurate to speak of a gene for perceiving intoxication as desirable than to speak of a gene for alcoholism as such.

If intoxication was perceived as unpleasant because of the existence of another enzyme genetically unrelated to the genes for "alcoholism," then the existence of the intoxication gene, and the promoter gene resulting in valuing intoxication, would be biologically meaningless, because of the overriding effect of the dysphoric response gene. There would then be no such thing as alcoholism. If intoxication was experienced as unpleasant, then it would be in effect a psychological diarrhea, and alcohol would be avoided, despite the presence of all the other genetic machinery for alcoholism. Alternatively, if Ex-Lax was psychoactive, reductionists would postulate the existence of a gene for Ex-Laxism. The presence or absence of an addictive reaction to a food or drink may be accidentally related to its primary biological processing, to the genetics of that processing, and to its primary psychological effect. If there was no gene for suffering, there would be no addictions.

There are other problems with the hypothesis that there is a single gene or group of genes for alcoholism. The prevalence of alcoholism in our culture is far too high, given its survival disadvantage, for it to be inherited the way truly genetic diseases are. Additionally, the expression of the gene, if it exists, is *entirely* dependent on the existence of alcohol. If man had never discovered alcohol, there would be no alcoholics, and no one would be talking about the disease of alcoholism or its gene. This simple fact is always overlooked in endogenous biomedical reductionist models of alcoholism; it has to be, because the fact destroys the model. Alcoholism cannot be a primarily genetically driven condition like Huntington's chorea because Huntington's chorea occurs no matter what human beings are doing culturally, as do Tay-Sachs disease and Lesch-Nyan syndrome. Once one has the gene for one of these illnesses, it will inevitably be expressed as a full disease syndrome.

There cannot be a gene for alcoholism because there would be no way for such a gene to evolve prior to the invention of alcohol. In the absence of alcohol on the planet, it couldn't be a gene for *alcoholism*. Biological reductionists might respond that (a) the gene was always there, it simply wasn't activated in the absence of the environmental promoter, and (b) without the gene, the availability of alcohol does not cause alcoholism. This is to miss the point.

All human beings would die if the nitrogen content of the atmosphere rose to 98%. From this scientific fact, does one conclude that there is a gene for nitrogen toxicity, one that awaits the appearance of the promoter, and that there is an inherited illness called nitrogen toxicity? No; that conclusion is patently absurd. Alternatively, would the logic be less erroneous if one modified the definition of the illness to call it oxygen deprivation disease? The biological requirement of mammals for oxygen is genetically based, and all mammals die in the absence of oxygen, so why isn't suffocation defined as a genetic illness? What is the difference in logic between oxygen deprivation disease and alcoholism?

For political, financial, and ideological reasons, not because of logic or science, alcoholism is placed in the category of biomedical illness while oxygen deprivation disease is viewed as an obviously absurd construct. There cannot be a gene for alcoholism in the simplistic way postulated by biological psychiatry. Alcoholism is the behavioral outcome of an accidentally related set of circumstances: (a) the invention of alcohol, (b) the fact that alcohol causes intoxication, and (c) the fact that in-toxication is highly valued by some human beings. The first cause is purely environmental, and second is biologically true of all human beings, and the third is the only possible genetically specific factor. Yet the third factor is the only one that is clearly psychosocially and culturally determined, as demonstrated by extensive evidence from the social sciences and by common sense. Do traveling salesmen drink more and eat more French fries than control groups because of genetic illnesses called alcoholism and French frieism, which drive them into this occupation? Isn't it likely a scientific fact that more people die from the long-term biomedical consequences of eating fast food than of

alcoholism in North America? Why is there no inherited disease of fast food consumption? This does not occur because decisions about what gets conceptualized as a biomedical illness within psychiatry are entirely socially determined.

Laboratory Tests Can Improve The Accuracy Of Psychiatric Diagnoses

Early in my residency, which lasted from 1981 to 1985, supervisors were frequently ordering dexamethasone suppression tests (DSTs) as part of their diagnostic workup of clinical patients, in the belief that a positive result would support a diagnostic conclusion of a mood disorder. I would guess that throughout North America tens of millions of dollars must have been spent on clinically useless, pseudoscientific DSTs in the first half of the 1980s. The test, heralded as psychiatry's first blood test for mental illness, was regarded as a window into the pathophysiology of depression - depression, in turn, being conceptualized as a genetically based biomedical illness.

Analysis of the logical fallacies inherent in this pseudoscientific enthusiasm led me to publish an editorial in *Biological Psychiatry* (Ross, 1986) pointing out the cognitive errors inherent in this misuse of the DST. I was surprised at the minimal reaction this paper generated, even though it struck at the heart of pseudoscience in biological psychiatry, and I cannot gauge its influence in the complete disappearance of clinical use of the DST in psychiatry by the early 1990s. A sociologist ought to conduct a detailed inquiry into the rise and fall of the DST, a history that reveals a great deal about the ideology and politics of reductionist psychiatry.

A simple analysis can demonstrate that the DST cannot have clinical utility as a diagnostic test for depression. Three diagnostic groups have to be considered in the analysis: (a) clearly clinically depressed, (b) intermediate cases such as schizoaffective disorder, and (c) clearly not clinically depressed. For each of these three cells there are two subcells, positive DST and negative DST, making a total of six cells.

For individuals who are showing no signs of depression, not even pseudodementia or masked depression, the DST can be of no clinical utility because no treatment for depression will be instituted regardless of the results. A positive result will be defined as a false positive (rate about 5%), and a negative result as a true negative. Neither result can influence diagnosis or treatment. In individuals who are unequivocally clinically depressed, the DST will not affect treatment because they will get an antidepressant, cognitive therapy, or some other treatment for depression regardless of test results. Positive DSTs will be defined as true positives (about 66%) and negative results as false negatives.

This leaves only the intermediate, clinically ambiguous group. In this group, a negative DST cannot be interpreted because there is no way to determine whether it is a true or false negative, therefore a negative result cannot influence either diagnosis or treatment. This leaves only one cell out of six in which the DST has possible clinical utility, the diagnostically uncertain group with a positive test.

It is precisely in this group that a positive result cannot be used without undermining the scientific foundation of the DST. If a positive result is regarded as a true positive, then there is no way to determine the false positive rate for the DST, and the reliability and validity of the test as a diagnostic tool for depression are destroyed. This means that the DST cannot be used in the only clinical group for whom it might be useful, and therefore it has no clinical utility.

I began to mentally catalog the errors of logic in biological psychiatry as I heard them from supervisors, encountered them at meetings, and read them in the literature. I learned that a complex network of interlocking cognitive errors is active in biological psychiatry, the totality of which supported the pseudoscientific use of the DST in the 1980s. Also, I observed that the enthusiasm for the DST disappeared from clinical psychiatry very quickly, while the underlying errors of thinking continued unchallenged. The rise and fall of the DST was never discussed; enthusiasm moved from the DST to PET scans.

This logic concerning the DST applies to all biological tests for all mental illnesses. The dream of biological psychiatrists is that an "objective" laboratory test for one of the major mental illnesses will be discovered, and that this will place psychiatry on equal footing with internal medicine, while eliminating the vagaries of syndromic, phenomenological psychiatric diagnosis. This dream is logically unsound and can never be realized. Although biological psychiatrists speak of *external validation* of psychiatric diagnoses by laboratory findings and specific markers, this can never happen. Why?

One problem has to do with signal detection and systems theory. An individual, let us say, suffers from the biomedical illness of schizophrenia. How does the psychiatrist know this? The only possible way to notice that a person suffers from schizophrenia is to observe behaviors and signs and listen to the report of symptoms, which support the diagnosis. The only standard by which it is possible to decide that an individual has schizophrenia is clinical, therefore the reliability of the concept of schizophrenia is limited by the kappa value for the clinical or structured interview diagnosis, which is in the range of 0.65-0.70.

Biological psychiatrists talk as if a blood test or brain scan could increase the kappa for schizophrenia to 0.95, but this is scientifically impossible. They believe that a specific abnormality in a brain scan, cerebrospinal fluid value, or blood test could provide an *external objective* measure that is more precise than clinical diagnosis. This is not possible because the biological signal emitted by the system and detected in the lab test is no more external to the system or “objective” than the behavioral signals. There is a fallacy that if a machine measures a biological signal emitted by a system, that is a more scientific and precise measure than direct observation of behavior. This is an ascientific reductionist cognitive error; it is not true methodologically or statistically. The error is caused in part by a scientifically naive faith in gadgetry.

Imagine that one tried to use a brain scan for diagnosing schizophrenia; the same problem would arise as in use of the DST: how could one decide which results are true positives and which are false positives? The only way to do this is by clinically assigning subjects to the categories of schizophrenic or non-schizophrenic. Once the scan results are used to make these assignments, the reliability, and therefore the validity of the laboratory test is destroyed. The lab test can never increase the kappa for the diagnosis because of this problem with false positives.

The only solution to this problem, from a bioreductionist perspective, is to propose that the lab values be the diagnostic criteria - by this logic, everyone with an abnormal test result has schizophrenia, regardless of clinical findings. If the lab test detects an abnormality that can be corrected with drugs, then the normalization of the lab value becomes the measure of successful treatment outcome, again regardless of clinical findings. According to this logic, it would be possible to be diagnosed and treated successfully for schizophrenia without ever having had any psychiatric symptoms. The potential for political abuse of such a psychiatric system is considerable.

The use of such lab tests would be impractical because it would be a waste of finite biomedical resources to screen for and treat a “disease” in a population with no symptoms. There would be no meaningful way to decide whom to test other than making clinical diagnoses, which returns us to the problem of false positives. The dream is analogous to the treatment of hypokalemia by internists, except that internists don’t attempt to remove the clinical findings from the loop, and they have a better grasp of the concept of clinically spurious false positive findings. Another tack proposed within biological psychiatry is to find biological markers for mental illnesses that can be detected prior to the onset of clinical symptoms and therefore can be used for preventive interventions in childhood or, the ultimate dream, in utero through abortion or genetic engineering. This potential use of laboratory tests in psychiatry is confounded by the same problem with false positives, except that the question is who will develop the category of schizophrenia in the future, rather than who has it in the present.

A destructive impact on the scientific quality of clinical psychiatry might occur if enthusiasm for the pursuit of markers and lab tests draws too much energy away from research on reliable phenomenological diagnosis, because this could potentially result in a drop in the kappas of diagnoses made in the clinic, which would in turn reduce the ceiling value for the reliability of any blood test. Biological psychiatry is absolutely dependent on the scientific rigor and precision of clinical diagnosis, and there is no way around this. Advances in biological psychiatry cannot occur without reliable diagnoses. The dream that there can be a genetic analysis or lab test with a perfect 1:1 fit with psychiatric clinical disease is actually a nightmare, and it cannot be pursued in the full waking state. The logical outcome of this sociology, if it was pushed to its extreme, would be psychiatrists functioning as totalitarian mind-control police, screening the population for “illnesses” and “treating” them with drugs and genetic engineering, irrespective of clinical reality.

The Physician’s Role Is To Treat Biological Illnesses

Reductionist biomedical psychiatry is supported by a network of tautologies, of which the dogma about the physician’s role is one. Here we have not just philosophical or ideological issues at stake, but major variations in the actual clinical behavior of psychiatrists. The point is best illustrated if we take two polarized extremes within psychiatry: (a) the private practice psychoanalyst, and (b) the state-employed biological psychiatrist. I will deliberately use extreme examples. The psychoanalyst has a caseload of 20 or fewer patients, each of whom is seen for an hour per contact, and many of whom are seen five times per week. The biological psychiatrist, on the other hand, has an average face-to-face encounter time of five to ten minutes, and sees 30 to 50 patients a day. These appointments are medication follow-ups with schizophrenics, manic-depressives, and other patients with major mental illnesses.

The appointment book of the biological psychiatrist looks like that of the average family physician, who sees about 40 patients a day; the appointment book of the psychoanalyst appears to represent a completely different profession! Part of the purpose of the reductionist ideology is to provide a rationale for the average appointment duration of the biological psychiatrist. If psychiatrists provide primarily psychotherapy for psychosocial problems, it makes no sense to see 40 people for ten minutes each in a single day, because the patients cannot possibly derive any benefit from such encounters. For such an appointment book to make sense, psychiatric disorders

must be defined as primarily biological in nature, with the psychiatrist's adjustment of medications as the only necessary, meaningful, or effective intervention he or she makes - "supportive counseling" can be done by devalued paraprofessionals such as social workers.

Although the reductionist psychiatrist may pay lip service to the value of psychotherapy when pressed, and may claim to do psychotherapy, in reality psychotherapy is reduced to common sense-based counseling, psychoeducation about mental illness and medication side effects, and reassurance.

Further, the psychiatrist's superior status in the mental health hierarchy depends on the dogma that the most serious illnesses are biological in nature, which helps maintain the income differential between psychiatrist and social worker. If the physician's role in our society was to treat spiritual problems with shamanic interventions, the ideological platform of the biological psychiatrist would be severely endangered and would not be able to borrow from the prestige of medicine.

Because psychiatrists are the only mental health professionals who are physicians, they have greater expertise in diagnosis and treatment of biomedical mental illnesses, but this is not how the greater expertise of psychiatrists is actually marketed. The marketing is done through allegiance to a biopsychosocial model, and the claim is that psychiatrists have the most *comprehensive* expertise and are therefore best qualified to head the mental health team. In practice, what actually happens is different, however: the bioreductionist psychiatrist restricts his or her activity to diagnosis and prescribing medication, and implicitly (or explicitly, at times) belittles the rest of the team as dealing with minor matters. This would not be possible if the physician's role was not defined as treating biological illnesses.

A related logical error in biological psychiatry is the idea that psychosis is more biological than neurosis. The sociological component of the error serves a turf-definition function within the mental health field, and helps to identify certain disorders as predominantly medical in nature and therefore requiring the unique skills of the psychiatrist. The key disorders are schizophrenia and the mood disorders, especially bipolar mood disorder and psychotic or endogenous depressions. These are the psychiatric turf *par excellence*, and therefore are most targeted for biomedical reductionist definition. The neuroses, on the other hand, tend to be regarded as less severe, less biological in nature, and therefore more suitable for the treatment efforts of psychologists and social workers. The criterion by which these illnesses were selected as the primary property of psychiatry had nothing to do with any scientific data about biological etiology; it was solely one of symptom severity. The responsiveness of these disorders to neuroleptics, lithium, and antidepressant medication only reinforced the already established selection of them as the intrinsically psychiatric illnesses.

A profound and disparaging psychiatric chauvinism is inherent in biological psychiatry, because all other mental health professionals are implicitly defined as junior in status and expertise. The neuroses are reduced to *problems in living* and are not included in the category of *disease*, which belittles them as constructs and belittles those who suffer from them. Alternatively, when any bioreductionist attention is paid to the neuroses, the ideological bias can be reversed, and the neuroses can be regarded as minor biological illnesses, although this is not the predominant implicit stance of biological psychiatry.

The corrective cognition is that mildness of symptoms and/or impairment does not in any way imply a less biological etiology. The severity-implies-biology error of biological psychiatry would be viewed as a preposterous doctrine if proposed anywhere else in medicine. The common cold is a biomedical illness with a specific etiology (this is true despite the fact that a number of different viruses can cause the common cold). The common cold is no less biological in nature than cancer of the pancreas. To stretch the point somewhat, one might argue that the basic etiology of a fatal gunshot wound is entirely psychosocial in nature, because the prevalence of this cause of death is profoundly affected by the availability of firearms in a given population. One might mount a similar argument about motor vehicle fatalities caused by drunk drivers, none of which would occur if either alcohol or cars were absent in a culture. Immediate causes of death may be far less biomedical in nature than the common cold.

Another related cognitive error is the belief that biological psychiatry is closer to medicine than psychological psychiatry. This error serves a particular, focused purpose - the exclusion of psychologists, psychiatrists' main competitors, from senior rank in the mental health field. The division created within psychiatry between biological and psychological psychiatry is in part an artifact of the effort to exclude psychologists from the social, political, and financial advantages of physician status.

Psychologists, in turn, have made strategic end runs around psychiatry in the past two decades, and have begun developing direct consultation relationships with internists and surgeons. Part of their strategy has been to use terms like *behavioral medicine* and to offer expertise in behavioral analysis and therapy, which psychiatrists tend to lack. These maneuvers and counter-maneuvers are all political in nature, on both sides. Defining biological psychiatry as closer to medicine has had a major impact on the distribution of research money within psychiatry. A clear hierarchy is in place, with psychiatry at the bottom of the totem pole within medicine, biological psychiatry at

the top of the totem pole within psychiatry, and psychosocial psychiatry at the bottom overall. Defining biological psychiatry as closer to medicine depends on a prior reductionist definition of medicine, which takes us to the model currently dominant within medicine as a whole.

The medical model as the term is currently used in our culture, actually means the bioreductionist model of medicine, which is only one of many possible models. Others include ancient Chinese, Greek, and shamanic medical models. By calling the bioreductionist model *the medical model*, reductionists imply that all medical models other than their own are not medical. They call their own particular model of medicine *the medical model*, then define all other models as superstitious, primitive, prescientific, or otherwise unworthy. With this sleight of hand, the prestige of thousands of years of medicine is appropriated by the bioreductionists, and everyone else becomes a fringe practitioner.

The political power of biological psychiatry depends on its cultural context and is rooted in the dominant ideology of industrialized medicine. Depending on the perspective of the analyst, modern medicine could be characterized as atheistic, male chauvinist, or mechanistic-reductionist. If the dogma that biology is more real than psychology did not dominate medicine at large, biological psychiatry could not borrow the prestige of medicine to bolster its ideology, because doing so would weaken its position.

The Genetic Basis Of Schizophrenia Is Scientifically Established

Dr. Pam demonstrated, in Chapter 1, that research into the genetic foundation of schizophrenia is inconclusive. The genetic basis of schizophrenia has not been scientifically established, even at a preliminary level. In fact, some key findings in schizophrenia studies are the opposite of those predicted by a genetic model, such as a greater incidence of schizophrenia in second-degree than in first-degree relatives. It would be difficult to find a clearer example, at any time in the twentieth century, of substandard pseudoscience dominating the ideology of a field.

The concordance of monozygotic versus dizygotic twins for schizophrenia is a chief example of how preconceived ideology drives the interpretation of findings: these results argue as strongly for environmental as for genetic etiology. Yet the results are always cited by bioreductionists as evidence supporting the heritability of schizophrenia. This skewed interpretation can be disavowed, on challenge, which is another example of the plausible denial-like organization of the reductionist conceptual system. In practice, the reductionist cites the twin studies as conclusive evidence of the heritability of schizophrenia and reduces psychosocial factors to pathoplastic influence only.

This argument is made by bioreductionists in sequential steps. First, the fact that the lifetime prevalence of schizophrenia is about 1% worldwide is interpreted as evidence that schizophrenia is a biomedical, genetically driven disease evenly distributed throughout the human race. This epidemiological fact could as easily be interpreted as evidence of the universal impact of certain basic characteristics of human culture. Having noted the 1% incidence and mentioned the twin and adoption studies, the reductionist will go on to acknowledge that culture plays a role in affecting the *content* of delusions and hallucinations; for example, schizophrenic African tribesmen tend not to have delusions about the CIA or about being controlled by gyroscopes implanted in their brains. The reductionist will then emphasize that the *structure* or *form* of the delusions is constant across cultures, because structure is a direct expression of the biomedical foundation of the disease. The bioreductionist thus maintains the illusion of a biopsychosocial approach while reducing psychosocial factors to the content level. Content, however, is no more important in biomedical schizophrenia than in delirium, and the same drugs are prescribed no matter what the content. The psychosocial domain is acknowledged, then robbed of any clinical importance. The draining of clinical significance out of the psychosocial realm is the reciprocal strategy of its diversion into the biological and is evidence of the pseudoscientific nature of biological psychiatry. Undermining the psychosocial would not be necessary if the biological actually had a solid scientific foundation. If there actually was a scientifically established genetic basis to schizophrenia, there would be nothing for biological psychiatrists to be defensive about, and therefore no need to belittle psychosocial variables.

The ideological war within psychiatry about the dogma of biological psychiatry is itself evidence of the pseudoscientific nature of biological psychiatry. Within internal medicine, in comparison, there is no ideological conflict about the etiology of Tay-Sachs disease, because its genetic basis has been conclusively established.

There is another confound in the reductionist argument - the fact that bioreductionist psychiatrists cannot differentiate schizophrenia from dissociative identity disorder, clinically or in their research. The 1% prevalence of schizophrenia worldwide is probably not a fact, because the prevalence of false-positive schizophrenia probably varies proportionally to the prevalence of false-negative dissociative identity disorder. If this is shown to be the case by epidemiological studies that take dissociative disorders into account, bioreductionists

will be undisturbed, because they will then argue that schizophrenia is a genetic illness unevenly distributed around the world. This would be the only possible reactive position for them to take.

The Dopamine Theory Of Schizophrenia Deserves To Be Called A Theory

The dopamine theory of schizophrenia is a point of pride in biological psychiatry. It is not a theory, for several reasons. In my experience, nonmedical mental health professionals are usually surprised when I explain to them that the dopamine theory of schizophrenia was arrived at in reverse. What do I mean by this? The dopamine theory was built up in the following sequence of steps. First, it was serendipitously noticed that the phenothiazines have antipsychotic properties in humans, and they were used clinically with dramatic results.

Second, it was established in rat brain preparations that the antipsychotic drugs are postsynaptic dopamine receptor blockers. They block the neurotransmitter effects of the brain's dopamine. In the third step, it was concluded that because neuroleptics reduce psychosis and block the effect of dopamine, psychosis must be caused by an overactivity of the dopamine system. This reasoning was then given the title, the dopamine theory of schizophrenia.

This is a different process from the development of the theory of relativity, and it belongs to a different category of intellectual function. The theory of relativity and the dopamine theory of schizophrenia can-not meaningfully be placed in the same category, with both called scientific theories.

The bioreductionist response might be that I am proposing an elitist definition of a scientific theory, attainable only by rare geniuses. That is untrue. If I reviewed several books on the history of science, I could enumerate dozens of examples of scientific theories, major and minor. I am saying that the dopamine theory of schizophrenia does not belong to that *category*.

The naming of the dopamine theory of schizophrenia is a political strategy. One could not so easily obtain a grant to study the *dopamine idea of schizophrenia* or even the *dopamine model of schizophrenia*. Calling it a theory makes it, and the field, sound more high-falutin' and scientific but is really a semantic sleight of hand. Psychiatry does not have an adequate theory of any kind. It has various biological ideas, but no biological theories.

The dopamine hypothesis in schizophrenia is scientifically interesting and is worthy of serious scientific study. To call it a theory, though, is a cognitive error. Current interest in psychiatry is focused on presynaptic serotonin uptake blockers and the serotonin hypotheses that flow from them. The actual phrase *serotonin theory* is not used, however, partly because this class of medication is effective for so many different categories of mental illness. The *serotonin theory of depression, obsessive-compulsive disorder, posttraumatic stress disorder, some aspects of borderline personality disorder, trichotillomania, and other disorders*, does not have a good ring to it, and if used would threaten to expose the cognitive errors in the conceptual system. Drug companies market new psychotropic medications on the basis of the serotonergic action of their products, but they too have avoided the phrase *serotonin theory*.

Depression Is Based On A Biological Deficit, Likely Of Serotonin Or Noradrenalin Function

The history of noradrenalin and serotonin models of depression is interesting and is related to the dopamine theory of schizophrenia. The idea that depression is based on a biological deficit comes from the observation that depressed people are low on energy, plus bioreductionism. A severely depressed person is like a record playing at slow speed, with reduced energy, slowed movements, a reduced range of body movement, slowed thinking, a reduced range of facial expression, and little interest in things. The intuitively obvious conclusion is that the depressed person is low on something: the thinking that led to biological deficit theories of depression is no more sophisticated than this. Combined with the deficit theory of depression is an excess theory of mania, because mania is the clinical opposite of depression. The fact that antidepressants sometimes switch a depressed bipolar patient into mania is consistent with this model.

Biological excess models of mania are not emphasized to anywhere near the degree of deficit theories of depression, however. One reason is that neuroleptics, which block dopamine, are effective for treating mania but do not induce depression in bipolar patients. The same is true of lithium, which brings a person down out of mania, but not up from depression: lithium holds a responsive bipolar patient in a normal mood state on a long-term basis. Lithium does not interact with receptors and so does not fit into the receptor-transmitter models that dominate biological psychiatry. Additionally, cognitive therapy of depression is as effective for the treatment of nonpsychotic unipolar depression as antidepressants. These clinical facts do not fit into a simple model. It is logically possible that depression results from an excess of something that slows you down, and mania from a deficit, but these models are rarely if ever

mentioned in biological psychiatry.

When I was a resident, during the DST era, the focus in biological psychiatry was on noradrenergic deficiency states as the cause of depression, with the DST tied into the neurotransmitter regulation of the hypothalamic-pituitary-adrenal axis. Then it was discovered that serotonergic antidepressants are also effective in depression, so there was excited discussion about the possibility of noradrenergic and serotonergic subtypes of depression. Researchers measured levels of noradrenalin, serotonin, and their metabolites in the blood, urine, and cerebrospinal fluid of depressed patients, and tried to predict response to one or the other type of antidepressant based on the results. The results were contradictory, inconclusive, and all over the map.

One could have normal levels of noradrenalin, high levels of noradrenalin metabolite, and respond to a serotonergic antidepressant; or high levels of serotonin, low levels of serotonin metabolite, and respond to a noradrenergic antidepressant. For some years, supervisors identified the really first-rate residents by which ones had the antidepressants memorized according to whether they were noradrenergic or serotonergic, but this rating system quietly disappeared when the data failed to support it.

This would appear to be an example of proper scientific hypothesis making and testing, but it is not. Ideological enthusiasm for serotonin has far outstripped the interest in noradrenalin, with the development of fluoxetine and other serotonin reuptake blockers, which have a broad spectrum of action and a low side-effect profile. The fact that these drugs block serotonin presynaptically is clinically incidental.

If noradrenalin and serotonin were really being looked at dispassionately within biological psychiatry, rather than on the basis of hype and marketing buzz, there would be more comment on the fact that noradrenergic antidepressants are equally effective as serotonergic ones for many disorders in the affective spectrum, thereby destroying the specificity of serotonin hypotheses. The enthusiasm is driven by drug company marketing tactics and by the fact that the new serotonergic agents are more specific for serotonin receptors than noradrenergic drugs are for noradrenalin receptors, and therefore have fewer side effects. This is an accident of pharmacological history and has nothing to do with the biology of mental illness.

The marketing of buspirone is a good example of drug company strategies and their acceptance by biological psychiatry. When I was involved with buspirone in Phase III drug trials in 1984, the drug company's predominant emphasis was on the dopaminergic actions of the drug, with little mention of its serotonergic properties. Two things caused this emphasis to flip 180 degrees: (a) clinicians became worried about possible neuromuscular side effects of buspirone because of their experience with neuroleptics, and (b) serotonergic drugs like fluoxetine began to take a major market share in future projections. In reaction to these two developments, the dopaminergic properties of buspirone were completely dropped from discussion by the drug company, and the serotonergic properties were emphasized exclusively. This had nothing to do with any discoveries about the biology of mental illness; it was a clever marketing strategy leading to biological psychiatry's ignoring the dopaminergic properties of the drug and speaking only about its serotonergic actions.

Someone who had not been on the inside of this history would see only the progression of normal science, not realizing that the biological deficit model of depression is based on simple reasoning, drug company marketing, and no good data. There is no scientific evidence whatsoever that clinical depression is due to any kind of biological deficit state. Yet, like the heritability of schizophrenia, the deficit model of depression is regarded as established - a given, within biological psychiatry, unless directly challenged.

The Placebo Response Is An Artifact Of No Intrinsic Interest

I recall being present at a drug company-sponsored marketing consultant dinner for which I and the other psychiatrists attending were paid \$500 each (and given a free meal). The drug company was presenting video and brochure material for the marketing of a new product, and wanted consumer feedback from the psychiatrists. The company also presented slides of the multicenter, double-blind, randomized, placebo-controlled trial showing that their product was as effective for the target disorder as the standard medication already on the market. Symptom response curves for the two drugs showed a visually dramatic drop in symptom levels on a standardized measure. It was a typical drug company protocol with no methodological problems, and there was animated discussion of the pros and cons of the glossy brochures and computer-generated animation on the video.

During the latter part of the evening, I raised my hand and earned my \$500. I suggested that, because the curve for placebo also took the same degree of dramatic drop on the slide of treatment response, they might want to consider de-emphasizing that slide in their marketing, and focus instead on the equivalent efficacy of their product compared to the other medication; anyone who noticed the placebo curve would be unlikely to be impressed by the need to prescribe a medication no more effective than placebo. The drug

company representatives were polite and thankful for my feedback, both publicly, and privately after-ward, because they have good marketing skills.

In biological psychiatry, the placebo response is a major anomaly that is almost entirely ignored, although it poses a fundamental bio-logical problem. When I say “ignored,” I mean ignored as a serious scientific puzzle of paradigm-threatening proportions. The placebo-responsiveness of major depressive episode illustrates the major role of the placebo effect in biological psychiatry. Placebo is a powerful psychotropic medication, and causes considerable side effects in double-blind trials. Not everyone realizes that placebo causes a measurable number of side effects - I have had subjects drop out of double-blind studies because of placebo side effects, and I have had subjects randomized to placebo experience a 90% drop in symptom levels. This is a common experience in drug trials.

During my residency, a major rationale for prescribing the anti-depressants that I was taught to give patients was that the natural history of depression is that it tends to last six, nine, or more months before it remits spontaneously. By taking an antidepressant, it would be possible to be better in a few weeks, thereby avoiding the many months the patient, if untreated, would have to wait for spontaneous remission. At the same time, I learned that in a six-week drug study for depression, 70% of people would respond to a standard antidepressant and 30% would respond to placebo. Nobody ever pointed out the problem with the arithmetic: far too many people get better on placebo within the first two to three weeks of drug trials for spontaneous remission to get all the credit.

If major depressive episode is a biological illness, how can it so often be cured by placebo? This problem is simply ignored by biological psychiatry. The percentage of subjects who do not respond to the “active” antidepressant is about the same as the percentage who respond to placebo, in any large antidepressant drug trial. This is a well-established fact. One might conclude from these data that 30% of clinically depressed individuals have a nonbiological form of depression unresponsive to antidepressant medication.

More importantly, it is always said in psychiatry that 70% of depressed people will get better if given an antidepressant. This is true but deceptive. Of the people who get better on an active antidepressant, 30% are actually doing so because of a placebo response, not because of the chemical properties of the medication. This means that, overall, only 50% of clinically depressed patients get better when given an antidepressant drug because of the chemical effects of the drug, and 30% would get better on placebo. This is not so impressive a gap. If one defined antidepressant non-responders as suffering from nonbiological depressions, this would be half of all patients. Doing so would be as logical and reasonable as the inverse assumption made by biological psychiatry: that response to medications is an indication of biological etiology.

If one did a cost-benefit analysis of medication versus placebo based on the 50% to 30% differential, taking into account the side effects and the deaths from overdose, the cost benefit for tricyclic antidepressants would be very modest. Such calculations are never made by bioreductionists because they are ideologically unfavorable. The cost benefit for the newer serotonin uptake blockers would be more positive because of their lower side-effect profile.

Thirty percent of every treatment response obtained by biological psychiatry is due to the placebo effect. Yet the placebo effect receives virtually no research funding in and of itself within psychiatry. This does not make scientific sense.

I learned about the clinical power of the placebo effect as a second-year medical student, when I was learning how to start I.V.s and draw blood gases. I was doing rounds with the technologist, who advised me that the next patient was the most difficult person to draw gases from in the hospital. The patient was a six-year-old asthmatic girl in an oxy-gen tent who became very upset, frightened, and uncooperative every time blood was drawn, which was daily. Because of her size, the blood had to be drawn from the femoral artery.

I told the girl that I had a special anesthetic with me that I would rub on her before I stuck the needle in, and this would completely take away the pain, so that she would feel nothing. The agent worked perfectly - the little girl was completely calm, felt no pain, said thank you, and smiled when I was finished. The anesthetic agent was an alcohol swab. The failure to systematically study and augment the placebo response, because it does not fit with reductionist ideology, is depriving many people of symptom reduction they could otherwise receive. This is not good medicine.

If the placebo response was carefully studied and was augmented to the maximum possible level, the gap between antidepressants and placebo might narrow to nothing. This would happen if the placebo response rate was 40%, because the specific drug effect would then also be 40%, given that only 60% of the 70% of subjects responding to medication would be experiencing a pharmacologically based effect. Systematic study and augmentation of the placebo effect by only 25% would eliminate the difference between placebo and antidepressants in the treatment of depression.

Biological Psychiatrists Treat Chemical Imbalances In Their Patients' Brains

I have listed this cognitive error separately because the phrase *chemical imbalance* is so widely used by biological psychiatrists and their patients. On many occasions, I have listened to a patient tell me that his or her doctor is treating him for a chemical imbalance.

Patients with reductionist, chemical-imbalance models of their psychiatric disorders seldom want to do any psychotherapeutic work, because the reductionist model has reinforced their denial and has led them to conclude, "It's not my fault." Such patients often take a passive role in treatment and are difficult to engage in any kind of working partnership. They want to be told what to do and what pills to take, and they believe the doctor knows best. Paradoxically, receiving a reductionist countertransference response of this sort may actually be the best thing for such patients, and the cognitive errors of biological psychiatry may actually help hold them together, although the effect is attributed to the irrational polypharmacy, through an attributional error. The chemical imbalance model may be quite appropriate and helpful for a pure lithium-responsive, bipolar mood disorder patient, but the model gets overgeneralized to patients with borderline personality disorder, eating disorders, dissociative disorders, and a wide range of other psychiatric difficulties. These people need to be active participants in their treatment, in a way that is very different from the requirement to take lithium regularly, and they must take psychological responsibility for their problems in order to get better. The most medical treatment in psychiatry is the chemical and surgical reassignment of transsexuals, yet biological psychiatry as such has contributed nothing to this treatment, which is done primarily by endocrinologists and surgeons. It is ironic that the one psychiatric disorder that is actually treated by rebalancing chemicals in a medically rational manner, is of minor interest to biological psychiatry.

Note: this chapter was written while gender identity disorder was still defined as a mental disorder based on the 1980 DSM-III criteria - in DSM-5 (2013) the diagnosis was changed to *gender dysphoria* and being trans was no longer in and of itself a mental disorder - the disorder was conflict and bad feelings about being trans, not being trans in and of itself.

Finding A Biological Factor In A Mental Illness Will Make It More Real And Valid

The dogma in biological psychiatry is that biology is more real than psychology. From this follows the cognitive error that any biological findings specific for a mental illness will make it more real. This cognitive error mirrors the professional chauvinism of the relationship between physics and biology: biologists are dismissed by reductionist physicists as dealing in the soft epiphenomena of underlying physical processes. In reaction to this, biologists feel inadequate, dream of eventually tagging biology to observations at the level of quantum physics, and do not share in the prestige of physics within the Faculty of Science. The same chauvinist division exists between experimental and theoretical physicists, with the experimental physicists being viewed as engineers and lab technicians by the theoreticians.

The search for a biological component to mental illness also occurs in a hierarchy of levels. The most fundamental and sought-after prize is a gene, because in the reductionist hierarchy, the gene is the ground floor of psychology. Less valued is a *marker*, which means any biological abnormality specifically related to a given psychiatric disorder. Markers are in turn divided into those that are intrinsically related to the core pathophysiology of the illness, and those that are more accidentally related. At a psychiatry conference, the speaker with incomprehensible slides and vocabulary from genetics is most intimidating to the audience.

A real biological finding in psychiatry would not necessarily be of any fundamental interest. It might consist of no more than filling in a blank. For instance, it is obvious that there must be a brain neurotransmitter that regulates pain. Before the endorphins were isolated (which was not done by a psychiatrist), the transmitter could have been called *pain regulatron*, without any knowledge of its structure or receptor. It has made no difference to clinical psychiatry that we can now use the word *endorphin* instead: for psychiatry, this is merely a semantic substitution. We don't understand pain any better within psychiatry because we now know that the pain regulatron is an endorphin; we have no new treatments, and nothing has changed in the life of any psychiatric patient.

To many, this will seem like a preposterous argument or an indication that I oppose scientific progress. But those reactions would be mistaken. It is a good thing that the endorphins were discovered, and the discovery was part of the desirable and proper progression of normal science.

Imagine that the genetics and physiology of the brain had been completely described from a biomechanical point of view, leaving no work to be done on the biology of the brain. We would be no further ahead in understanding the mind-body problem. We would not understand *pain*. We would understand all the biological correlates of pain, and could manipulate pain clinically with greater precision, but we would not understand where the subjective perception of pain comes from, because we would not have located the connection between mind and body.

Reductionist science deals with this problem by dismissing the mind as an unreal epiphenomena and defining the problem as a non-problem, which is the only possible strategy open to reductionism. Where in the biological machinery does the *pain* come from? Does the pain spring into the mind from the receptor, from the axonal transport molecules, from the electrical charge in the neuron, from the vesicles, or from the synaptic cleft? This is an absurd question with no answer; it is absurd because the connection between mind and body cannot be localized in Newtonian space. The mapping of Newtonian space, which is the program of reductionist science, can never result in an understanding of the mind.

The truth is the other way around: only clinical psychiatric findings can make biological factors real in psychiatry. A biological finding is by itself meaningless unless it correlates with a problem in the *mind*, which is the domain of study of psychiatry. Without the mind, without clinical symptoms and human suffering, there could be no field called psychiatry. There would be only mammalian brain physiology and mechanistic neurology. The drive of reductionist biomedical psychiatry is to destroy psychiatry by making the mind irrelevant. Psychiatry is being taken over by other mental health professionals, because psychiatrists are focusing on biological pseudoscience and the pursuit of the impossible. A map of the brain is worth nothing without a map of the mind. If it were not for the subjective perception of pain, there would be no reason to even look for the endorphins, and if isolated, they would be biologically meaningless.

Biological Psychiatrists Have Made Important Discoveries About Mental Illness In The Past Ten Years

Biological psychiatry has not made a single discovery of clinical relevance in the past ten years, despite hundreds of millions of dollars of research funding. The argument in this section can be conducted by placing the burden of proof on biological psychiatry to describe a single finding derived from the bioscientific work of psychiatrists that has had any direct clinical utility or application.

Bioreductionist psychiatry maintains its funding position based on hype and the promise of future results. Claims that we are in the decade of the brain, that major discoveries are just around the corner, or that the latest brain scan or blood test is of fundamental interest, have been highly successful marketing strategies for biological psychiatry, but are cognitive errors. Biological psychiatry has conducted by far the most successful marketing campaign, in terms of research dollars, political power, and prestige, ever mounted by psychiatry, yet most bioreductionists would probably disavow participation in any kind of marketing scheme and would claim to be scientists and academics. This claim is itself part of the marketing strategy.

Bioreductionist psychiatry has adopted the position that it is closely allied with mushrooming developments in the brain sciences, nuclear medicine, molecular biology, and other sciences. However, none of the fundamental developments in these other fields has been due to the work of psychiatrists, and biological psychiatry has borrowed the techniques and methods of other fields for application to psychiatric patients. For instance, the MRI scan was developed entirely outside psychiatry, then psychiatrists used it to scan the brains of individuals they had placed in different DSM-IV categories, looking to see if the computer would find any differences. Such research does not require any creative scientific thinking; it simply involves running psychiatric subjects through preexisting technologies and protocols. One has to look far and hard to find original, creative, scientific thinking conducted within the boundaries of biological psychiatry by psychiatrists, a situation radically different from that in molecular biology, where ingenious experiments abound.

As far as the development of new psychiatric medications is concerned, biological psychiatry can take little credit for the advances made. I have been a drug company contractor in a number of different Phase III multicenter, double-blind, randomized, placebo-controlled trials, have been to Europe twice at drug company expense, have published the results of drug trials as first author, have been a paid speaker for drug companies in four different cities, and have been on about ten drug company-sponsored trips within North America. I have participated in trials of neuroleptics, antidepressants, and anxiolytics, and have published an original neuroanatomical and neurotransmitter model for the use of buspirone in tardive dyskinesia. Based on this experience, I conclude that psychiatrists are contract technicians in new drug development, not creative scientists.

The development of a new psychiatric medication takes at least ten years and \$100 million. The selection of drugs for study in humans follows the synthesis of new agents by chemists, who use a procedure called *chemical roulette*. This involves making minor chemical modifications to known drugs or simply trying out new molecules based on educated speculation. Once these chemicals are synthesized and purified, they are tested in animals to see whether they affect the animals in the way known antidepressants, neuroleptics, or anxiolytics do. Standardized animal models have been developed by chemists and rat psychologists for this purpose; none of the models has anything to do with the research findings of biological psychiatrists. Biological psychiatry as such has no role in

the development of drugs up to the point of testing in humans.

Once human studies are initiated, no creative thinking is required from biological psychiatry. The protocols are drawn up in a highly standardized fashion based on the requirements of the Food and Drug Administration (FDA) and its equivalents around the world. Although some psychiatrists are in the loop at this point, no creative thinking of a scientific nature is required from them. After the protocols are set, psychiatrists are recruited through industry contacts to conduct the trials. The psychiatrists, at most, contribute a few minor modifications of the protocols.

Why are psychiatrists required at all? The reasons are technical, logistical, and political. *Scientifically*, there is no need for biological psychiatry in the development of new psychotropic medications. The drug companies need academic psychiatrists by decree of regulatory agencies, which insist that there be a contractual, arm's-length relationship between the physicians conducting the trials and the company with the patent. This is a proper and necessary arrangement. Additionally, psychiatrists are required logistically, but not scientifically, for patient recruitment. This is also a good financial arrangement: physicians can be employed contractually on an as-needed basis, without being company employees. The contractual arrangement reduces research and development costs for psychiatrists to zero during periods in which no drugs of a given class are under development.

Drug company contracts, now a major source of research income for medical schools and biological psychiatrists, are used to finance a large amount of other research. There is nothing wrong with this, and I used such contracts to finance my own research. There is a pressing need for new drug development. The new serotonin reuptake blockers are a major and highly beneficial development for psychiatric patients, and I prescribe them regularly - for dissociative identity disorder patients, among others. There is no disputing the fact that these medications are more effective than placebo.

The medications do not come from biological psychiatry, however; they come from drug companies that employ psychiatrists as contract technicians. Psychiatrists are a politically and logistically indispensable part of the loop, as they should be, but their contribution to the process is not that of creative scientist. The advances in psychopharmacology during the second half of the twentieth century cannot be attributed to a scientific effort by biological psychiatry, although biological psychiatry should get full credit for its technical achievements.

A possible objection to this reasoning would be that biological psychiatrists have been responsible for innovative applications of medications in psychiatry, such as the use of anticonvulsants like valproic acid and carbamazepine in certain psychiatric conditions. This argument would actually reinforce my position, rather than provide a counter-argument. Borrowing drugs from neighboring disciplines and trying them out on different DSM-IV categories is the clinical equivalent of chemical roulette, requires no creative scientific thinking, and is a secondary industrial application of an already manufactured product.

Overlooking the distinction between secondary technical applications and original scientific discovery has been a key strategy in the marketing of biological psychiatry.

The Ascendancy Of Biological Psychiatry In The 1980s Has Resulted In A More Scientific And Effective Psychiatry

Biological psychiatry depends on an ahistorical perspective, which it fosters in psychiatry residents. A not uncommon attitude is to regard anything written before 1970, or even 1985, as antiquated and pre-scientific. Even when that attitude is softened and a hat is tipped to Kraepelin, it is still said that over 90% of the serious writing in the field has been published since 1980. This is a manifestation of the grandiosity that pervades the field: bioreductionists think of their field as exploding scientifically like molecular biology, with major advances in the understanding of brain physiology, fundamental new findings arising from brain scan research, and revolutionary new clinical applications due shortly, especially in genetic engineering. They view the field as having taken off exponentially since 1980, with most developments before that being of "historical" interest only. In reductionist language, "historical" is a condescending and dismissive term, like the popular phrase "of academic interest only." Both phrases mean that the problem under discussion is of no real importance and can be consigned to the ivory tower.

A dogma of biological psychiatry is that symptoms of serious mental illness are a direct expression of primary physical pathology in the brain. Even in an illness with a predominantly endogenous-biological etiology, this need not necessarily be the case. The depression of Cushing's syndrome when the problem originates in the adrenal glands, the anxiety of hyperthyroidism, and mental status changes in paraneoplastic syndromes are good examples of biomedical psychiatric disorders accompanied by normal brain physiology. This

is the case in the sense that changes in brain physiology in these disorders are secondary to pathophysiology elsewhere in the body: given the abnormality elsewhere in the body, the brain's response is biologically normal and the genetics of the brain are normal. It is theoretically possible that the primary abnormality in schizophrenia is in the gastrointestinal tract, and that the abnormality causes absorption of a protein, which in turn produces psychosis. The emphasis on primary brain pathophysiology is not a necessary postulate of bioreductionist psychiatry.

The second aspect of this cognitive error is that causality within the brain-mind field is unidirectional in reductionist psychiatry. The third is the directness of the causality, even in instances in which the direction of the arrow is correct. Given the complexity of the brain, the number of transductions of signal that occur between the primary biological defect and the symptoms is likely considerable. Production of a psychiatric disorder by the brain is probably like the production of a commercial airline disaster, in that multiple unrelated factors must come together to produce the final outcome. These factors may be no more directly related to each other in the brain, biologically speaking, than wind shear, metal fatigue, and pilot error are intrinsically related to each other in nature.

The linear model of scientific development, as readers of Thomas Kuhn (1962) know, ignores the widely accepted thesis that scientific progress occurs through discontinuous paradigm shifts. Here we find another paradox in the conceptual system of biological psychiatry: bio-logical psychiatry acts as if it has initiated a paradigm shift, when actually it is an example of "normal pseudoscience," a term I just coined. In normal science, an established paradigm dominates a given field, and researchers within the field work comfortably within the paradigm. Minor discrepancies in research findings are easily explained away as artifacts or errors until, gradually, enough anomalous data accumulate that the entire paradigm is threatened.

At this point, a discontinuous intellectual and creative leap is taken by the leaders of a new school of thought, and there is a paradigm shift. The new paradigm gradually takes over the field, and established adherents of the old school have to literally die out before this can occur. During the transition period, there is ideological warfare. A key feature of the new paradigm is that it can account for all the data and observations understood within the old perspective, while also encompassing the anomalous data that drove the shift. The classic example of a paradigm shift is the transition from Newtonian to relativistic physics.

Once serious mental illness is defined as always biological in nature, the cognitive error that biological research offers the only real hope for victims of major mental illness becomes a tautology and is regarded as self-evident. The tautology feeds back on other reinforcers of the differential flow of research money, prestige, and academic appointments to bioreductionists, and maintains the pseudoscientific paradigm intact.

Dissociative identity disorder is a major piece of anomalous data threatening this cognitive error. At this point in the history of psychiatry, the dissociative disorders have the status of anomalous data, and a paradigm shift to a trauma model of psychopathology has not occurred. Dissociative identity disorder is a major mental illness by all criteria for that category, including severity of symptoms, morbidity, impact on psychosocial function, economic cost to society, and, probably, mortality. The paradigm shift has not occurred yet because an insufficient quantity of anomalous data has accumulated to date.

Dissociative identity disorder is the only major mental illness about which we can make any of the following statements:

We understand its etiology, which is the dissociative response to chronic childhood trauma;

We understand at a microdetailed level the relationship between the etiology and the phenomenology, and we can relate the signs and symptoms of the disorder to a detailed understanding of structure within the organism;

We have a microdetailed understanding of the specific relationship between the phenomenology and the treatment interventions;

The disorder can be cured with currently available methods;

We understand all the requirements for primary, secondary, and tertiary prevention (although we lack the political will).

All of these statements are true at a psychosocial level of analysis. The pathophysiology of dissociative identity disorder is not understood in anything but the most speculative, preliminary fashion, which is not surprising, given that bioreductionist researchers do not acknowledge the reality or importance of the disorder and do not devote research resources to it.

From a public health point of view, I believe the contribution of diagnostically specific genes for mental illness, even if they exist, occurs in a small number of pedigrees and accounts for a minute fraction of psychiatric morbidity and mortality. Comparatively,

serious chronic childhood trauma is the overwhelming major driver of psychopathology in Western civilization. This estimation can be tested with currently available structured interviews and epidemiological methods. The bulk of psychopathology in our culture represents the normal human response to chronic childhood trauma, based on a normal genetic endowment. This is entirely analogous to evidence in what used to be Yugoslavia: the bulk of current morbidity and mentality is due to physical trauma and is based on normal genetic endowment and the normal response of the human organism to environmental insult.

If my viewpoint (which is not unique to me) is correct, then biological psychiatry in its current form is a major diversion of resources in the wrong direction, and these resources need to be redirected to the normal psychobiology of trauma. Here, they would quite quickly yield biologically and clinically meaningful findings rooted in mammalian physiology, within a biopsychosocial paradigm. Reductionist biological psychiatry cannot study the normal biology of psychosocial trauma without destroying itself; therefore, it does not do so.

Biological Psychiatrists Are Good Diagnosticians

Many biological psychiatrists are poor diagnosticians either because of (a) poor application of DSM-IV rules or (b) proper application of the diagnostic rules, which themselves are full of contradictions and cognitive errors. The DSM-IV system is one of the truly important achievements of twentieth-century psychiatry, and it far outweighs the contribution of biological research. I am a firm believer in the necessity for operationalized diagnostic criteria. Nevertheless, the DSM-IV diagnostic system arises from the reductionist philosophy of late twentieth-century North American psychiatry, although it takes the position of being aphistorical and phenomenological, not realizing that the decision to be phenomenologically based is itself a philosophical decision.

In the DSM-IV system, psychiatric disorders are largely treated as separate entities, consistent with the hypothesis that there is a gene for schizophrenia, a gene for depression, and another separate gene for alcoholism. Although there are groupings of disorders, and various exclusion rules based on the presence of other disorders, the main purpose of the system is to sort patients out into discrete categories. The way in which diagnoses are placed in categories, rather than being phenomenologically based, is highly determined by historical artifacts, the residual effects of Freudian theory, and political turf disputes among different subcommittees.

For instance, in DSM-IV, conversion disorder is classified as a somatoform disorder and is grouped with hypochondriasis and body dysmorphic disorder, with which it has no natural relationship. This reflects the influence of Freudian ideas about somatization and conversion, and the simple fact that all disorders in the somatoform section have something to do with the body. In the *International Classification of Diseases-10* (ICD-10), however, conversion disorder is classified as a dissociative disorder and is grouped with psychogenic amnesia, which is a much more logical, naturalistic, and phenomenologically based location for it. For some reason, European nosologists have grasped the dissociative nature of conversion disorder and have not been politically trapped into grouping conversion disorder with hypochondriasis.

In DSM-IV, dissociative identity disorder (DID) is an exclusion criterion for dissociative disorder not otherwise specified (DDNOS): one can receive a diagnosis of DDNOS only if one does not meet criteria for one of the other defined dissociative disorders. However, in ICD-10, which comes from Europe, where there is far less acceptance of the concept of DID, DID is still called multiple personality disorder and is listed as a form of DDNOS. These differences in classification are entirely ideologically based and have nothing to do with any scientific data or phenomenological approach to nosology.

The history of brief reactive dissociative disorder, a diagnosis invented during the DSM-IV process, is also instructive. This entity was constructed primarily by Robert Spitzer and David Spiegel to capture trauma-induced dissociative disorders of short duration, and was accepted favorably by the DSM-IV committee examining the dissociative disorders, of which I was a member. Where does this diagnosis appear in DSM-IV? In the anxiety disorders section, with its name changed to *acute stress disorder*. How did this happen?

The first problem with brief reactive dissociative disorder was that, after a month's duration, if it had not remitted, the diagnosis changed to posttraumatic stress disorder (PTSD), which is classified as an anxiety disorder. This would mean that a patient would switch *categories* of mental illness at the end of a month, which made no sense. If brief reactive dissociative disorder was to be preserved, and the switch to PTSD after one month was to be preserved, there were only two possible solutions to the problem: (a) move PTSD to the dissociative disorders or (b) move brief reactive dissociative disorder to the anxiety disorders. The decision to move brief reactive dissociative disorder to the anxiety disorders was based solely on the greater political power of the anxiety disorders group compared to the dissociative disorders group. Once the switch was made, it was necessary to change the name of the disorder, because one cannot have an anxiety disorder called brief reactive dissociative disorder. This was done.

How is acute stress disorder defined in DSM-IV? Criterion A is the experience of a trauma. Criterion B lists five dissociative symptoms, of which one must have three:

1. Subjective sense of numbing, detachment, or absence of emotional responsiveness;
2. Reduction in awareness of one's surroundings;
3. Derealization;
4. Depersonalization;
5. Dissociative amnesia, that is, an inability to recall an important aspect of the trauma.

Criterion H is a generally worded exclusion criterion: "Not due to the direct effects of a substance (e.g., drugs of abuse, medication) or a general medical condition, and is not merely an exacerbation of a preexisting Axis I or II disorder." The other criteria include avoidance behavior, a duration criterion, and intrusion and hyperarousal criteria; the intrusion symptoms are dissociative in nature.

There are no specific diagnostic rules for how to differentiate acute stress disorder from dissociative amnesia disorder, depersonalization disorder, and DDNOS. What we have is a dissociative disorder placed in the anxiety disorders section for political reasons, then defined as if the dissociative disorders section did not exist. This is also true of PTSD, which is much more logically grouped with the dissociative disorders than with simple phobia and obsessive-compulsive disorder. The *phenomenology* of PTSD, as defined in the DSM-IV diagnostic criteria, is far more like that of the dissociative disorders than the other anxiety disorders. The pretense to a purely phenomenologically based diagnostic system is transparently false.

There is a similar problem with the DSM-IV rules for diagnosing schizophrenia: they are designed as if DID doesn't exist. There are five criteria for schizophrenia. Criterion A is the presence, for at least a month or two, of the following:

1. Delusions;
2. Hallucinations;
3. Disorganized speech (e.g., frequent derailment or incoherence);
4. Grossly disorganized or catatonic behavior;
5. Negative symptoms (i.e., affective flattening, alogia, or avolition).

Note: Only one A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices are conversing with each other.

The other four criteria involve social/occupational deterioration, presence of the illness for at least six months, and ruling out schizoaffective disorder, mood disorder with psychotic features, substance abuse, and general medical conditions as causes of the symptoms.

Clinically, every DID patient I have ever met meets criterion A, most meet criterion B (the dysfunction criterion), all meet criterion C (the duration criterion), and all meet the exclusion criteria. The diagnostic rules of biological psychiatry result in a false positive diagnosis of schizophrenia in 100% of DID cases in which there is social/occupational deterioration. If DID affects 1% of the general population (Ross, 1991) and at least 5% of general adult psychiatric inpatients (Ross, Anderson, Fleisher, & Norton, 1991; Saxe et al., 1993), then the DSM-V schizophrenia group will have only two responses open to it: act as if DID doesn't exist, or radically modify the diagnostic criteria for schizophrenia in DSM-V, and include DID in the exclusion criteria and the text.

I have included these examples of political decisions in DSM-IV because they refute the proposition that biological psychiatrists are good, scientific diagnosticians, because I know the history firsthand, and because the politics illustrate the paradigm-threatening nature of dissociative identity disorder. It might be objected that the DSM-IV system and biological psychiatry are two separate things, and that problems with DSM-IV cannot necessarily be blamed on bioreductionists. Although this is true in theory, in reality the system is driven by bioreductionist assumptions and ideology.

As I mentioned previously, DID is a test case demonstrating that bioreductionist psychiatrists cannot differentiate a disorder they consider to be hysterical and artifactual from a disorder (schizophrenia) they consider to be a biomedical brain disease. This differential diagnostic inadequacy has had a direct and major impact on the lives of hundreds of thousands of people in North America.

Biological Psychiatry Is Bringing More Respect To Psychiatry

This cognitive error has depended on a dissociation of biological psychiatry from other sectors of the mental health field, with disavowal of culpability for the dissociation by biological psychiatry, and a substantial degree of amnesia for it. In certain sectors of the mental health field, bioreductionism is creating scorn and loss of business for psychiatry. This is best illustrated by feminist, community-based master's level therapists who treat sexual abuse survivors with psychotherapy. The scorn is militant and mutual.

The bioreductionists take the stance of being rational and scientific, and they denigrate the psychotherapists for being impressionistic, hysterical, and poorly trained. The therapists, on the other hand, deal daily with the effects of hostile and sadistic countertransference toward their clients, sexual exploitation of them, rude behavior, minimally helpful polypharmacy with numerous side effects, and condescending attitudes toward the therapists. Not all biological psychiatrists are like this, but many are. The therapists complain about the great difficulty they have finding psychiatrists who will prescribe rationally for their clients, not interfere destructively in their cases, and support their clients' recovery. Most of the therapists are female, and most of the biological psychiatrists are male.

During my residency, I didn't realize the size of the chasm between academic psychiatry and the rest of the mental health field. As part of my residency, I had virtually no contact with nonacademic mental health professionals based outside the teaching hospital system, except for case workers on child and adolescent cases. I had no idea how towered the ivory tower actually is, and I had a vague impression of community-based therapists being feminist, antiscientific, and poorly trained. When, as a staff psychiatrist, I started to work predominantly with sexual abuse survivors (they comprised over half the clientele of the department, but there was no teaching on sexual abuse in my residency), I began to work closely with community-based therapists, and found the bioreductionist stereotype to be confirmed in some instances. I met female therapists who were anti-male, anti-hospital, anti-scientific, anti-medical, anti-medication, anti-DSM, and anti-me, and I could not work with them.

However, I found a majority of skilled, conscientious, well-educated therapists who were keenly interested in supervision, consultation, and continuing education. They had infinitely more expertise in the long-term sequelae and treatment of childhood sexual abuse than biological psychiatrists, and were doing excellent work for low wages with few resources. These therapists were inundated with the treatment failures and casualties of bioreductionist psychiatry.

As a strategic plan for the next ten years, investment in bioreductionism by psychiatry, I predict, will further alienate psychologists and master's-level therapists from psychiatry, will reduce the domain of psychiatry, will divert resources away from psychiatry into the trauma model, and will bring psychiatry into further disrepute. This is a prediction I would never have made had I stayed insulated in academia. Because it is a sociopolitical prediction, it cannot be a compelling argument. Time will tell.

Conclusion

These errors of logic in biological psychiatry can all be corrected, and none is essential to a scientific psychiatry. I have enumerated them in the hope that the destructive influence of reductionism and pseudo-science within psychiatry will thereby be modulated. Biological psychiatry could be a fascinating and important field, if it was shorn of its pervasive cognitive errors and if its academic standards were higher.

As a logic system, the conceptual system of biological psychiatry is organized in a fashion similar to the personality systems of patients with dissociative identity disorder. The tautologies, positive feedback loops, closure to alternative hypotheses, pervasive overgeneralization, use of dissociation to eliminate cognitive dissonance, and other structural and functional properties of the system maintain it in a dysfunctional homeostasis. Given that this system responds to cognitive and systemic interventions in the individual dissociative identity disorder patient, one can be hopeful that it will do so within bioreductionist psychiatry. The main factor that militates against this possibility is the massive amount of secondary gain experienced by biological psychiatry in North America in the late twentieth century.

References

- Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression*. New York: Guilford Press.
- Kaplan, H. I., Freedman, A. M., & Sadock, B. J. (1980). *Comprehensive textbook of psychiatry/III*. Baltimore: Williams & Wilkins.
- Kuhn, T. (1962). *The structure of scientific revolutions*. Chicago: University of Chicago Press.
- Ross, C. A. (1986). Biological tests for mental illness: Their use and misuse. *Bio-logical Psychiatry*, 21, 431-435.
- Ross, C. A. (1991). Epidemiology of multiple personality disorder and dissociation. *Psychiatric Clinics of North America*, 14, 503-

Ross, C. A., Anderson, G., Fleisher, W. P., & Norton, G. R. (1991). Frequency of multiple personality disorder among psychiatric inpatients. *American Journal of Psychiatry*, 148, 1717-1720.

Ross, C. A., & Leichner, P. (1986). Canadian and British opinion on formulation. *Annals of the Royal College of Physicians and Surgeons of Canada*, 19, 49-52.

Ross, C. A., Leichner, P., Matas, M., & Anderson, D. (1990). A method of teaching and evaluating formulation. *Academic Psychiatry*, 14, 99-105.

Saxe, G. N., van der Kolk, B. A., Berkowitz, R., Chinman, G., Hall, K., Lieberg, G., & Schwartz, J. (1993). Dissociative disorders in psychiatric inpatients. *American Journal of Psychiatry*, 150, 1037-1042.

Szasz, T. (1974). *The myth of mental illness*. New York: Harper & Row.

Walker, J., Norton, G. R., & Ross, C. A. (1991). *Panic disorder and agoraphobia. A comprehensive guide for the practitioner*. Pacific Grove, CA: Brooks/Cole.

Research Open

Pseudoscience In

The American Journal Of Psychiatry 1991-1993

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The American Journal of Psychiatry, the Official Journal of the American Psychiatric Association, has been published continuously since 1844. It is now under the editorship of Nancy C. Andreasen, M.D., Ph.D., who is the eleventh editor of the journal; the immediate past editor, from 1978 to 1993, was John C. Nemiah, M.D. The *Journal* appears monthly, and a full annual volume occupies about 1,800 pages. Each issue contains a variety of Special Articles, Editorials, Regular Articles, Brief Reports, Letters to the Editor, Book Reviews, and other material. The *Journal* is the flagship publication of American Psychiatry and is one of a handful of top psychiatric journals in the world. It is broad in scope and includes research, clinical, and review papers on all areas of psychiatry. I coauthored four papers in the *Journal* from 1990 to 1993 (Ross, Miller et al., 1990; Ross, Joshi, & Currie, 1990; Ross, Anderson, Fleisher, & Norton, 1991; Carlson et al., 1993), and consider it to be the preferred place to publish psychiatric papers. I mention this to demonstrate that I am not in any way hostile to *The American Journal of Psychiatry*. I have chosen it for review in this chapter precisely because the *Journal* is eclectic, authoritative, and prestigious. Psychiatrists, including my-self, mention with pride papers they have published in “The Green Journal.”

My task in this chapter began with a review of all issues of the *Journal* for 1990 through 1993. I have drawn from this substantial body of literature illustrative examples of the logical errors, methodological flaws, and ideological biases of biological psychiatry. These illustrate the points made by Dr. Pam and myself in the previous chapters. For convenience, I have grouped papers into categories that illustrate each of these intellectual weaknesses. I have made no attempt to do anything other than provide examples of cognitive errors, and have not commented on sound papers. My purpose is to show that pseudo-science is endemic in biological psychiatry.

Statements Of Bioreductionist Ideological Bias

I include this category to demonstrate that direct statements of reductionist ideology can be found in the psychiatric literature. If this were not so, the thesis of this book would have to be that the bias is pervasive but entirely covert.

Wu, J. C., & Bunney, W. E. (1990). *The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis*. 147, 14-21.

The cognitive error that biology underlies psychology, and is the level of primary etiology, is evident in this sentence, “An intensive review of the phenomenology and mechanisms of action of sleep deprivation may provide important clues for understanding the underlying biological substrate of depressive illness and for the future development of rapidly acting antidepressant treatments or drugs.”

In their quite lengthy review article, the authors make passing note of the methodological limitations of this literature:

None of the 61 studies used a double-blind, placebo-controlled design because of the difficulty in ensuring that the subjects and the experimenters are blind to a manipulation such as sleep deprivation and in part because of the difficulty of finding a suitable placebo control. It is possible that the antidepressant response could be due to experimental bias expectations or the nonspecific effects of attention by the raters.

Sixty-one studies is a large amount of effort to expend without ever developing a research design that meets minimum scientific criteria. It is doubtful that a literature this low in methodology would support a long review article in a top journal in a rigorous scientific field.

Raine, A., Venables, P.H., & Williams, M. (1990). *Autonomic orienting responses in 15-year-old male subjects and criminal behavior at age 24*. 147, 933-937.

In this study, skin conductance and heart rate measures of orienting were obtained in 101 noninstitutionalized 15-year-old boys, and criminal status was determined 9 years later at age 24 (17 had a criminal record by age 24). The two groups differed significantly on the measures, leading the authors to conclude: “Given the strong evidence for the role of genetic factors in criminal behavior and

the fact that the psychophysiological variables in this study are in part genetically determined, it seems possible that the genetic predisposition to criminal behavior finds its expression to some degree through these autonomic nervous system factors.”

No such conclusions are warranted logically or scientifically; one would want to examine the cognitive errors leading to the conclusion that the measures have a demonstrated genetic component. This study will be referenced in other studies as evidence supporting the genetic foundation of criminal behavior, which is how the bioreductionist literature works: erroneous conclusions in one paper are used to support erroneous conclusions in others, and a network of confirmatory pseudoscience is constructed.

Pardes, H. (1990). Presidential address: Defending humanistic values. 147, 1113-1119.

The following paragraphs convey both the pervasive cognitive errors and the feeling tone of biomedical psychiatry, with lip service paid to the psychosocial:

Humanistic values are at the very heart of our profession. The study of the mind, and the healing of the mental anguish that can rob people of the fulfillment of their humanity, is our life's work. To this work we bring both our own humanity and the force of modern science.

The rewards can be enormous. In the past decade, especially, we have been dazzled by advances in brain imaging, molecular genetics, psychopharmacology, and other fields of study that have revolutionized neuroscience. The most exciting aspect of these advances is what they promise for our capacity as physicians. Because of this panoply of research-encompassing high-tech findings about the brain, evaluation of the psychotherapies, linkage studies, epidemiology and the refinement of diagnostic criteria, the discovery of effective medications, and the development of effective rehabilitation we can see and begin to deliver new kinds of relief for mental suffering. Few of us would have dreamed that these advances were possible in the days when we entered the field. It has been very moving to find that our progress is understood by our patients, their families, and our friends in the citizens' movement, who are now devoting their own considerable vitality and talents to the fight against mental illness.

In contradistinction to this rhetoric, the purposes of the present book are: to reduce the degree of dazzle in the contemporary mind, and to being the force of modern science to bear on biological psychiatry.

Sabshin, M. (1990). Turning points in twentieth-century American psychiatry. 147, 1267-1274.

This paper was delivered as the Adolph Meyer Lecture at the American Psychiatric Association Meeting in 1989. It contains a rare glimmer of critical thinking about the costs and excesses of bioreductionist ideologically logical enthusiasm, while remaining uncritical of the pseudoscientific nature of the “best stories” in psychiatry:

During this past decade, the best stories about psychiatry in print and electronic media have involved the scientific advances in the field. As these stories have increased, they have begun to offset the continuing negative stories and may be moving to a point where they will go beyond offsetting. The need to change the public image of psychiatry has also played a key role in producing the current turning point. For some of my research colleagues, this effect is passionately denied as if it meant that their work is designed to influence the public. Just the opposite is true; high quality work affects the public because it is high quality. But we must want to seek public support while reducing the stigma against patients and practitioners. In this process, a tendency to overcorrect for previous errors is inevitable. A focus on genetic markers for manic-depressive illness gets much more attention than stories about the less fashionable reports of successful psychotherapy. This attention and the resultant allocation of resources affect many segments of our training programs, certification procedures, and accreditation processes. The overreaction certainly has many practical consequences.

Faraone, S. V., Biederman, J., Keenan, K., & Tsuang, M. T. (1991). A family-genetic study of girls with DSM-III attention deficit disorder. 148, 112-117.

This excellent paper is almost free of ideological bias; yet, even here, acquiescence to biomedical reductionism appears. The authors commit the cognitive error of *if it runs in families it must be genetic* in their title and in this sentence: “The familial transmission of attention deficit disorder among families with a son who has the disorder provides external validation for the diagnosis in boys and suggests genetic influences in the disorder.” Such data suggest environmental influences just as much, but that is not the authors’ bias. Nor can such data provide external validation for a disorder: lying, malingering, and factitious disorders could all run in families.

Zorumski, C. F., & Isenberg, K. E. (1991). Insights into the structure and function of GABA-benzodiazepine receptors:

Ion channels and psychiatry. 148, 162-173.

This is a comprehensive and scholarly paper, and its solidity is derived largely from review of research done by nonpsychiatric biologists. In the final paragraph, the authors caution psychiatry (in sentences that do not follow each other logically) against simpleminded biological theories, but they are nevertheless committed to a bio-reductionist model of serious mental illness, one tied to receptor subunits rather than neurotransmitters:

Simple notions of increases or decreases in transmitter levels, metabolites, or receptors in a disease state will need to be tempered by an understanding of how such changes may affect each of the receptor subtypes in a given region. It is possible that specific disorders may reflect abnormalities of only a single receptor subtype. Thus, crude measurements of transmitter levels offer little hope of shedding light on pathophysiology. In addition, molecular genetic studies offer the opportunity of directly considering receptor subunit gene involvement in psychiatric disorders.

Winchel, R. M., & Stanley, M. (1991). *Self-injurious behavior: A review of the behavior and biology of self-mutilation.* 148, 306-317.

This paper contains 116 references of which 2 are on childhood sexual abuse, a major driver of self-mutilative behavior. Even when an over-whelming environmental factor is identified, however, the reductionist can invert it into evidence of primary etiology lying in the genetic domain:

Although the importance and grave traumatic effects of childhood sexual abuse should not be underestimated, a cause-and-effect relationship between abuse and self-injurious behavior should not be automatically assumed. Sexual abuse may serve to elicit symptoms in an individual already at risk, but frequent histories of such trauma may also reflect a familial pre-disposition to impulsive-and perhaps violent-behaviors. An interplay of both factors suggests the unfortunate possibility that those who are biologically endowed with a vulnerability to self-injurious behavior may also have a greater probability of being raised in a familial environment where the stresses that might elicit such behavior-such as childhood sexual behavior are more likely to occur.

The authors, without quite being direct, are proposing a genetically driven category of impulse control disorders, with the gene expressing itself as perpetration in the parental generation and wrist slashing in the victim generation. The gene causes the victim to become a perpetrator of her children, who also carry the gene, and who will cut them-selves as a result. This spectrum could be treated with selective sterilization.

Russell, J. L., Kushner, M. G., Bettman, B. D., & Bartels, K. M. (1991). *Non/fearful panic disorder in neurology patients validated by lactate challenge.* 148, 361-364.

This would be a good paper if the authors had not emphasized the cognitive error about external validation by biological tests in their title and their discussion: "Positive responses to lactate by these patients lend substantial credence to the nosological validity of non-fearful panic disorder as a panic disorder sub-diagnosis." Positive responses to psychosocial triggers of panic would be no less validating, but would not be as likely to result in the paper's being accepted at *The American Journal of Psychiatry*.

Volkow, N. D., & Tancredi, L. R. (1991). *Biological correlates of mental activity studies with PET.* 148, 439-443.

These are the only authors, in the four years of the *Journal* reviewed, who displayed any evidence of an ability to differentiate their bio-reductionist ideology from scientific method and logical analysis: "In interpreting these findings, one should also keep in mind the reductionism of this approach."

Swift, R. G., Perkins, D. O., Chase, C. L., Sadler, D. B., & Swift,

M. (1991). *Psychiatric disorders in 36 families with Wolfram syndrome.* 148, 775-779.

The authors believe: "Identifying genes that predispose individuals to psychiatric disorders and understanding their metabolic basis will lead, in many instances, to effective prevention or treatment measures for these disorders." Although *prevention* is usually supposed to imply some unknown but humane form of genetic engineering to be perfected in the next few decades, in fact it means abortion and sterilization.

Samson, J.A., Mirin, S.M., Hauser, S.T., Fenton, B.T. & Schildkraut, J.J. (1992). *Learned helplessness and urinary MHP levels in unipolar depression.* 149, 806-809.

I include this paper because the authors propose that a biological measure, urinary MHPG levels, could be used to differentially triage depressed clinical patients into psychopharmacology or cognitive-behavioral therapy. The authors demonstrate that bioreductionist bias is not intrinsic to biological psychiatry, and their proposal is a concrete example of how such bias would limit and restrict such research, because a reductionist would never make this suggestion. From a bioreductionist research team, we would expect instead speculation about different genetic subtypes of depression based on the same data.

Freedman, D. X. (1992). *The search: Body, mind, and human purpose*. 149, 858-866.

This paper was delivered as the 1991 Adolph Meyer Lecture at the American Psychiatric Association Meeting. It communicates the bedazzled state of contemporary psychiatrists, as did Pardes (1990) in his Presidential address, discussed above:

In all of medicine, for the bedazzled clinician the sweep and promise of modern science is, in fact, breathtaking. We should be appreciative but not mesmerized. For, in sobriety, we will have to determine which of the plethora of science leads to apply practically in the clinic and clinical research. The gap between visions of what may be and application is still huge but narrowing.

In another paragraph, Freedman combines correct caution and humility, on behalf of psychiatry, with the characteristic tone of biological reductionism:

Thus, for all our power to understand synaptic regulations, we are still calibrating precisely where and how brain substances and mechanisms are relevant to the manifestations of disease. We want to know whether brain receptors are different in the diseased patient-as they ought to be. We have truly enticing starts, some secondary pathophysiology, and a high index of suspicion as to genetics, but to be clear: clinically diagnostically specific, etiopathological definitions of our diseases remain an ultimate goal.

By the end of this chapter, the reader may wish to consider whether *calibrating* or *fishing* is the more accurate verb for characterizing psychiatric biological research.

Buckley, P., Stack, J.P., Madigan, C., O'Callaghan, E., Larkin, C., Redmond, O., Ennis, J. T., & Waddington, J. L. (1993). *Magnetic resonance imaging of schizophrenia-like psychoses associated with cerebral trauma: Clinicopathological correlates*. 150, 146-148.

This study has five subjects and eight authors. The authors state:

Four of our patients had no family history of schizophrenia, but an uncle of patient 1 had himself experienced a head injury prior to the onset of psychosis. The modest number of patients studied precludes definitive inferences as to genetic risk, but our findings are consistent with the idea that the risk for schizophrenia among relatives of patients with a schizophrenia-like psychosis is considerably lower than the risk in relatives of patients with schizophrenia.

The phraseology partially disguises the preposterous nature of the authors' comments.

Quitk in, F. M., Stewart, J. W., McGrath, P. J., Nunes, E., Ocepke-Welikson, K., Tricamo, E., Rabkin, J. G., & Klein, D. F. (1993). *Further evidence that a placebo response to antidepressants can be identified*. 150, 566-570.

The authors studied response to placebo and active medication in de-pression and concluded that rapid responses are placebo responses, and do not last as long as slower-onset true medication responses. They view more gradual-onset responses to placebo as true spontaneous re-missions. This is a biased viewpoint because rapid onset of anxiety to benzodiazepines and of psychotic agitation to neuroleptics is common-place, and both are regarded as true medication responses.

The most interesting implication of the paper, which the authors do not discuss, is the unavoidable conclusion, following from their line of logic, that the placebo plus spontaneous remission response rate must be subtracted from the apparent medication response rate in drug trials, in order to yield the true medication response rate, which will be much closer to the sum of placebo plus spontaneous remission. This is the argument I made in the preceding chapter.

Miller, L. J., O'Connor, E., & DiPasquale, T. (1993). *Patients' attitudes towards hallucinations*. 150, 584-588.

The ideological bias that extrasensory experiences are a symptom of mental illness is enshrined in the DSM-IV criteria for schizotypal personality disorder, and this false assumption confounds all studies of schizophrenia spectrum disorders. The idea that hallucinations

are always pathological, and presumably due to organic brain dysfunction, also pervades psychiatry and confounds research. The authors of this paper demonstrate these biases, and remark: "In medical practice, symptoms of an illness are usually assumed to be undesirable. It is notable, therefore, that more than one-half of the subjects in this study reported that their hallucinations served adaptive functions, and a sizable minority wished to continue experiencing the hallucinations."

The final sentence of the paper is: "The findings also suggest, but do not prove, that psychological factors contribute toward the expression of hallucinations in patients with psychotic illnesses." The possibility that hallucinations can be normal psychic phenomena, and not always pathological, is inconceivable to bioreductionist psychiatry, even when psychological factors are accepted. The paper illustrates pathologizing of normal human experience—a characteristic of contemporary psychiatry.

Faraone, S. V., Biederman, J., Lehman, B. K., Keenan, K., Norman, D., Seidman, L. J., Kolodny, R., Kraus, I., Perrin, J., & Chen, W. J. (1993). Evidence for the independent transmission of attention deficit hyperactivity disorder and learning disabilities: Results from a family genetic study. 150, 891-895.

This study could have been titled a family environmental study just as easily, because the methodology cannot differentiate genetic from environmental causes. The only reason to call it genetic is ideological bias, fueled by cognitive errors.

Cloninger, C. R. (1993). Unraveling the causal pathway to major depression. 150, 1137-1138.

Kendler, K. S., Kessler, R. C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1993). The prediction of major depression in women: Toward an integrated etiological model. 150, 1139-1148.

In an editorial that precedes the Kendler et al. (1993) paper, Cloninger (1993) states of the study: "It was possible to draw etiologic conclusions about both genetic and environmental influences because the sample included both monozygotic and dizygotic twins." The Kendler study was a major project, and worth doing; however, the genetic factors included in the study are entirely artifactual.

Kendler et al. explain:

The genetic liability to major depression was assessed by a dummy variable given the value of 0 if the co-twin had no history of major depression and 1 if the co-twin had had one or more lifetime episodes. This dummy variable was multiplied by 1.0 if the twin pair was monozygotic and 0.5 if the twin pair was dizygotic. This method of modeling genetic effects in a regression analysis assumes that the familial transmission of the liability to major depression is largely due to additive genetic effects (which are correlated perfectly in monozygotic twins but only 0.5 in dizygotic twins).

If monozygotic twins have environments that are purely equal, while those of dizygotic twins are only half equal, and if the causes of depression are purely environmental, a similar dummy variable could be constructed to yield an environmental contribution to depression. The "genetic factor" in this study is a pure artifact that confirms its own assumptions through a tautology. The analysis should be redone with the dummy variable removed. This study should never be cited as providing any evidence of any kind on the genetics of depression. It is a worthwhile study of environmental factors, but nothing more.

Oliver, J. E. (1993). Intergenerational transmission of child abuse: Rates, research, and clinical implications. 150, 1315-1324.

This is a good paper. I include it here because the findings and the literature review could have been used to support the idea that there is a gene for child abuse, given that child abuse is clearly familial. This would be the usual bioreductionist inference from such data. This inference is never encountered in the child abuse literature because that literature is not driven by reductionist ideology. The putative gene for child abuse could be used as a defense in a court of law.

Walker, E. F., Grimes, K. E., Davis, D., & Smith, A. J. (1993). Childhood precursors of schizophrenia: Facial expressions of emotion. 150, 1654-1660.

The authors studied the facial expressions of adult schizophrenics in home movies taken during their childhoods, and compared them to childhood home movies of their healthy siblings. The authors viewed the reduced frequency of expressions of joy in the children who would later develop schizophrenia as early signs of the illness: "[T]he fact that these occur in the domain of emotion suggests that constitutional vulnerability to schizophrenia has implications for affective functioning long before the onset of clinical symptoms."

One could just as logically conclude that the subjects had a constitutional predisposition to joylessness, and that the schizophrenia was a secondary psychosocial consequence of being born with this constitution in this culture, in these families. Alternatively, one

could simply conclude that the schizophrenics received less love than their siblings, which caused both their joylessness and their schizophrenia. The data cannot differentiate between these two hypotheses versus the one the authors chose on ideological grounds.

Stoll, A. L., Tohen, M., Baldessarini, R. J., Goodwin, D. C., Stein, S., Katz, S., Geenen, D., Swinson, R. P., Goethe, J. W., & McGlashan, T. (1993). *Shifts in diagnostic frequencies of schizophrenia and major affective disorder at six North American psychiatric hospitals. 150, 1972-1988.*

In this study, the authors found that diagnoses of schizophrenia declined from a peak of 27% of all diagnoses in 1976 to 9% in 1989, while major affective disorders rose from 10% in 1972 to 44% in 1990. The authors concluded: "Although a real decrease in new cases of schizophrenia may have occurred, this effect was probably minor and dominated by a larger shift of such diagnoses to affective categories." They also remarked: "The changes in the reported frequency of the disorders and their diagnostic criteria underscore the limited accuracy and usefulness of psychiatric diagnosis due to lack of knowledge of the etiological basis of major mental disorders."

The authors are saying that this major shift in diagnostic patterns was based predominantly on bias and ideology, not on science.

Goldman, S. J., D'Angelo, E. J., & DeMaso, D. R. (1993). *Psychopathology in the families of children and adolescents with borderline personality disorder. 150, 1832-1835.*

The authors measured psychopathology in the relatives of 44 child and adolescent patients with borderline personality disorder and the relatives of 100 comparison subjects without that diagnosis. They found more depression, substance abuse, and antisocial behavior in the borderline relatives. Then, making a characteristic bioreductionist assumption, they reach a conclusion that is not supported by their data to the least degree:

The impact of finding greater rates of family psychopathology associated with the diagnosis of borderline personality disorder in children is twofold. First, it suggests an associated biological diathesis. Numerous studies have shown that the rates of depression, substance abuse, and antisocial disorder are higher in the offspring of parents with those same disorders. We have demonstrated, for the first time, that children with borderline personality disorder appear to be at significant biological risk for the development of certain types of psychopathology.

Second, and harder to evaluate, is the impact of familial psychopathology on the developmental experiences of these children. (p. 1834)

In fact, the environmental influences on these children are much easier to study than the biological ones, and the authors present data on environmental factors but none on biology. However, the authors have developed a rationale for reducing even demonstrated environmental factors to a genetic basis. They postulate that abusive behavior by parents is genetically driven:

What appears to shine as a beacon through the foggy nature of this disorder is its association with abuse and parental psychopathology. This makes the next logical step the development of an etiologic hypothesis that is grounded in these factors. This hypothesis would initially build on the role of abuse and parental psychopathology in the development of the disorder in a biologically vulnerable population. It might then be refined to a more genetic type of critical environmental failure that, when combined with bio-logical vulnerability, would be an etiologic factor across a wide range of developmental circumstances. (p. 1835)

By this logic, parents abuse their children because they are genetically driven to do so, and children develop psychiatric disorders in response to their childhood trauma because of biological vulnerability. The environment is reduced to a mere vector of biological determinism, and biology has become destiny. Eugenics follows logically as a "treatment intervention" from this biogenetic model, although, in the twenty-first century, the genetic interventions are expected to be "refined," involving genetic engineering rather than sterilization or execution.

The Strongest Biological Findings Correlate With Symptoms, Not Diagnoses

The ideology of bioreductionist psychiatry is that depression, schizophrenia, and other illnesses are biomedically distinct and genetically driven. Decades of fishing for supporting data have yielded nothing of substance, however. The meaningful biological findings in psychiatry and general medicine demonstrate correlations between biological variables and psychiatric symptoms-not illnesses-and these symptoms can occur in many different disorders. This means that even the findings of biological psychiatry are destroying the ideology that dominates the field.

Marin, R. S. (1990). *Differential diagnosis and classification of apathy*. 147, 22-30.

In this review paper, the author notes that there is solid evidence for apathy occurring as a symptom of numerous biomedical illnesses, including Parkinson's disease, Korsakoff's syndrome, Huntington's chorea, progressive supranuclear palsy, akinetic mutism, delirium, dementia, Kluver-Bucy syndrome, hypoparathyroidism, the amotivational syndrome associated with chronic marijuana abuse, and a wide variety of drug toxicities. In psychiatry, apathy, when it occurs in schizophrenia, is considered to be a "negative symptom" of schizophrenia, and to have a specific genetic cause.

Jones, J. S., Stanley, B., Mann, J. J., Frances, A., Guido, J. R., Traksmann-Bendz, L., Winchel, R., Brown, R. P., & Stanley, M. (1990). *CSF 5-HIAA and HVA concentrations in elderly depressed patients who attempted suicide*. 147, 1225-1227.

This study compared the levels of metabolites of serotonin and dopamine in the cerebrospinal fluid of 12 depressed elderly people who had attempted suicide, 9 depressed elderly people who had not attempted suicide, and 7 controls. The study involves 28 subjects and 9 authors. The Bonferroni correction would eliminate all significant findings. There were no significant differences between the two clinical groups on any measures of psychopathology, including level of depression, but the suicidal group had lower levels of both metabolites. The implication drawn is that suicide is directly caused by a depletion of dopamine and serotonin, rather than by environmental stressors.

The biological finding therefore correlates with a *behavior* but not with diagnosis or level of symptomatology. One might object that this is not a strong finding, and argue that the paper should be included in the fishing expedition section.

Barta, P. E., Pearlson, G. D., Powers, R. E., Richards, S. S., & Tune, L. E. (1990). *Auditory hallucinations and smaller superior temporal gyrus volume in schizophrenia*. 147, 1457-1462.

The authors used MRI scans to measure different areas of the brain in 15 schizophrenics and 15 controls. They found a robust significant correlation ($r = 0.71$) between degree of difference in superior temporal gyrus volume (subjects versus controls) and degree of auditory hallucinations, but no significant correlation for somatic/ tactile, visual, or olfactory hallucinations, a finding consistent with what is known about the brain and language. The diagnostic specificity of this finding requires replication in other diagnostic groups—most interestingly, dissociative identity disorder. As they stand, the data support a relationship between a symptom and a biological finding, but not a relationship with a diagnosis.

Darko, D. F., Risch, S. C., Gillin, J. C., & Golshan, S. (1992). *Association of beta-endorphin with specific clinical symptoms of depression*. 149, 1162-1167.

Plasma endorphin levels were measured in 20 depressed patients and 23 controls, with no difference between groups. Within the pooled group of 43 subjects there were significant correlations between two clinical measures (psychic anxiety and phobia) and endorphin levels, out of five variables measured; out of the 20 depressed patients alone, there were significant correlations for three out of four (psychic anxiety, phobia, and obsessions/compulsions). The authors state in their discussion: "There were no significant correlations between beta-endorphin and the SADS interview items in the comparison group." One wonders whether the authors added the secondary analyses after getting a negative finding concerning their original hypothesis.

Goldman, M. B., Blake, L., Marks, R. C., Hedecker, D., & Luchins, D. J. (1993). *Association of nonsuppression of cortisol on the DST with primary polydipsia in chronic schizophrenia*. 150, 653-655.

The authors found that the DST was positive in 38% of 13 polydipsic and 5% of 40 nonpolydipsic schizophrenics ($X^2 = 6.9$, $df = 1$, $p < .01$ with Yates's correction). The same phenomenon might occur among nonschizophrenic subjects, if controls were included, confirming that the biological finding is diagnostically nonspecific.

Biological Fishing Expeditions With No Significant Findings

In a serious, developed scientific field, the pressure on journals to publish new findings leaves little or no room for studies with negative results. These either should not be published or should be included as letters to the editor, except for the occasional major failure to replicate an important previous piece of research. This is not the situation in psychiatry.

The American Journal of Psychiatry publishes numerous biological studies in which there are no significant results. This occurs because of ideological enthusiasm for reductionism, lack of critical thinking, an insufficient quantity of meaningful studies, and the mistaken idea that negative fishing expeditions are scientifically exciting. The gestalt of the published studies as a whole is a blunderbuss approach with every-thing possible (usually a neurotransmitter or hormone) being tested in every possible disorder.

It would be impossible to publish similar papers on topics to which mainstream psychiatry is ideologically hostile. Reviewers would simply dismiss such papers as meaningless because they contained no significant findings. In fact, significant findings that are ideologically offensive are more difficult to publish than insignificant results on favored and acceptable topics. The negative studies often have lengthy author lists.

Martinat, J-L., Pernon-Magnan, P., Huret, J-D., Mazoyer, B., Baron, J-C., Boulenger, J-P., Loch, C., Maziere, B., Caillard, V., Loo, H., & Sy rota, A. (1990). Striatal D2 dopaminergic receptors assessed with positron emission tomography and 76Br bromospiperone in untreated schizophrenic patients. 147, 44-50.

The authors did PET scans on 12 schizophrenics and 12 controls and found no differences in an indirect measure of striatal dopamine receptor density in the two groups. The discussion section of the paper occupies 216 lines.

Kaye, W. H., Ballenger, J. C., Lydiard, B., Stuart, G. W., Laraia,

M. T., O'Neil, P., Fossey, M. D., Stevens, V., Lesser, S., & Hsu, G. (1990). CSF monoamine oxidase levels in normal-weight bulimia: Evidence for abnormal noradrenergic activity. 147, 225-229.

The authors measured cerebrospinal fluid levels of HVA (a metabolite or breakdown product of dopamine), 5-HIAA (a metabolite of serotonin), and norepinephrine (also called noradrenalin) in 27 bulimics and 14 controls. These are currently fashionable neurotransmitters in psychiatry. They did 14 t tests and 14 Pearson correlations on their data, two of each kind of test being significant at $p < .05$. If they had applied the Bonferroni correction for multiple comparisons, there would have been no significant results, meaning that this paper belongs in the category of biological fishing.

The authors state in their introduction: "Theoretically, greater than normal noradrenergic activity or low serotonergic or dopaminergic activity could contribute to binge-eating." Without the Bonferroni correction applied, their findings were that there were no differences between bulimics and controls on dopaminergic and serotonergic activity, and that bulimics had lower noradrenergic activity than controls ($t = 2.24$, $df = 38$, $p < .03$)!

These negative findings did not constrain the authors from concluding: "We theorize that normal-weight bulimia is not a subtype of depressive disorder and should be considered an illness with a unique and characteristic neurobiological profile."

Pelonero, A. L., Pandurangi, A. K., & Calabrese, V. P. (1990). Autoantibodies to brain lipids in schizophrenia. 147, 661-662.

In this study, levels of autoantibodies to brain lipids in 38 schizophrenics were compared to those in 22 controls, with no significant findings.

Lopez, O. L., Boller, F., Becker, J. T., Miller, M., & Reynolds, C. F. (1990). Alzheimer's disease and depression: Neuropsychological impairment and progression of the illness. 147, 855-860.

As stated in the abstract, "The authors longitudinally evaluated the cognitive functions of patients with probable Alzheimer's disease who also met criteria for major depression and compared them with matched patients with Alzheimer's disease who were not depressed." They found "no significant difference in the pattern of neuropsychological deficits between the two groups." This study involved 10 subjects and 10 controls, and would have never been published in *The American Journal of Psychiatry* if the subjects had a disorder presumed to be nonbiological in nature.

Jenike, M. A., Baer, L., Summergrad, P., Minichiello, W. E., Holland A., & Seymour, R. (1990). Sertraline in obsessive-compulsive disorder: A double-blind comparison with placebo. 147, 923-928.

This drug study involved 10 subjects on sertraline and 9 on placebo. Findings were negative. The discussion is 196 lines long. Although this is a drug study, not a biological fishing expedition, I include it here because of the negative findings.

Tancer, M. E., Stein, M. B., Gelernter, C. S., & Uhde, T. W. (1990). The hypothalamic-pituitary axis in social phobia. 147, 929-933.

The authors compared 26 patients with social phobia and 26 controls and found: "There were no significant differences in measurements of T3, T4, free T4, or TSH between patients with social phobia and normal control subjects."

Andreasen, N. C., Swayze, V., Flaum, M., Alliger, R., & Cohen,

G. (1990). *Ventricular abnormalities in affective disorder: Clinical and demographic correlates*. 147, 893-900.

This study occupies 7 pages and has 73 references, yet the findings are negative. As stated in the abstract:

Ventricular-brain ratio was measured by CT scan in 24 bipolar patients, 27 unipolar patients with major depression, 108 schizophrenic patients, and 75 normal control subjects. The male bipolar patients had significantly larger ventricles, but the depressive patients did not. The findings suggest the possibility that ventricular enlargement in bipolar patients is independent of age, as it appears to be in schizophrenia, whereas in depressed patients it may be related to the aging process. Ventricular enlargement in bipolar patients was not related to relevant clinical correlates, such as response to treatment, history of substance abuse, history of ECT, or cognitive impairment.

There were no significant findings between diagnostic groups, which shows that, in this sample, there is no biological specificity to ventricular-brain ratios with respect to psychiatric diagnosis. The groups were therefore divided into male and female subjects and 8 comparisons were done (4 diagnoses X 2 genders). Of these, only one was significant at $p < .01$, but this would not survive the Bonferroni correction for multiple comparisons. Subsequent to this, another analysis with age as a covariate was done. The amount of speculation in the paper can be inferred from the abstract.

Mayerhoff, D. I., Lieberman, J. A., Lemus, C. Z., Pollack, S., & Schneider, B. S. (1990). *Growth hormone response to growth hormone-releasing hormone in schizophrenic patients*. 147, 1072-1074.

The authors compared growth hormone function in 10 schizophrenics and 5 controls: "No significant differences between the schizophrenic and control groups were found on any of the variables." The discussion section is quoted here in full because of its surrealistic quality:

The GH responses to GH-RH elicited in the control subjects and schizophrenic patients appear to be consistent with those reported in normal subjects in the endocrinologic literature. The data suggest that the pituitary somatotrophic cells in patients with schizophrenia are capable of normal GH responses when stimulated directly. The results of this pilot study are consistent with the hypothesis that pathology at a level above the pituitary affects GH responses to dopamine agonists in schizophrenia. However, these findings must be viewed as preliminary because of the low statistical power resulting from the small number of subjects. The importance of applying the method used in this study to a larger sample is that any abnormalities found in GH responses of schizophrenic patients can be better localized in the brain.

Besides confirming these results by the study of larger numbers of subjects, future research in this area should also use selective pharmacologic probes for possible neurotransmitters that regulate GH-RH secretion from the hypothalamus. These measurements of GH should be coupled with GH-RH stimulations of GH in the same subjects in order to obtain a more complete characterization of neuroendocrine function in schizophrenia.

For those who have only time to read the abstract, the authors' key conclusion is: "The results suggest suprapituitary dysfunction in schizophrenia, but replication in a larger study is required."

The authors are emphasizing the importance of the replication of their negative findings in one area of the brain based on the assumption that this means positive findings will later be confirmed elsewhere in the brain—in this instance, at a level above the pituitary gland. Logically, this is equivalent to stating that analysis of one quadrant of the haystack suggests that the needle must be in another quadrant, although replication is required. Positive morale and continued funding for such research depend absolutely on the conviction that there is a needle to find, which is a matter of faith, not empirical science.

Roy, A., DeJong, J., Ferraro, T., Adinoff, B., Ravitz, B., & Linnoila, M. (1990). *CSF gamma-aminobutyric acid in alcoholics and control subjects*. 147, 1294-1296.

Cerebrospinal fluid levels of GABA were measured in 53 dry alcoholics and 22 controls and did not differ.

Sharma, R. P., Janicak, P. G., Javaid, J. I., Pandey, G. N., Gierl, B., & Davis, J.M. (1990). *Platelet MAO inhibition, urinary MHPG, and leukocyte beta-adrenergic receptors in depressed patients treated with phenelzine*. 147, 1318-1321.

Various biochemical variables were measured in 36 depressed inpatients treated with phenelzine. Except for confirmation of the known fact that phenelzine reduces levels of monoamine oxidase, which is not a publishable result, there were no significant findings.

Flaum, M., Arndt, S., & Andreasen, N. C. (1990). *The role of gender in studies of ventricle enlargement in schizophrenia*:

A predominantly male effect. 147, 1327-1332.

Brain ventricle size was measured by MRI or CT scan in four different studies with a total of more than 200 subjects and 200 controls. There were no significant findings.

Mutchler, K., Crowe, R. R., Noyes, R., & Wesner, R. W. (1990). Exclusion of the tyrosine hydroxylase gene in 14 panic disorder pedigrees. 147, 1367-1369.

This genetic study yielded no significant findings in 145 individuals in 14 pedigrees, and this was conceptualized as an important exclusion.

Nelson, J. C., Mazure, C. M., & Jatlow, P. I. (1990). Value of the DST for predicting response of patients with major depression to hospitalization and desipramine. 147, 1488-1492.

The authors did dexamethasone suppression tests on 51 depressed patients treated with desipramine, and found no differences between DST-positive and DST-negative subjects in response to hospitalization or medication.

Bowers, M. B. (1991). Characteristics of psychotic inpatients with high or low HVA levels at admission. 148, 240-243.

The author measured pretreatment homovanillic acid levels in 85 psychotic inpatients and found only one significant result out of 25 different dependent variables measured separately in high and low HVA groups, with these two groups subdivided into male and female for all comparisons. This one significant finding, at $p < .05$ out of 100 analyses, is a chance finding.

Darko, D. F., Wilson, N. W., Gillin, J.C., & Golshan, S. (1991). A critical appraisal of mitogen-induced lymphocyte proliferation in depressed patients. 148, 337-344.

The authors measured in vitro proliferation of lymphocytes in reaction to stimulants called mitogens, using blood from 23 depressed patients and 23 controls. There were no significant differences between the two groups. They conducted numerous nonsignificant secondary analyses on various subgroups of subjects, and got one spurious statistically significant finding on a subgroup of 10 patients.

Garver, D. L., Bissette, G., Yao, J. K., & Nemeroff, C. B. (1991). Relation of CSF neurotensin concentrations to symptoms and drug response of psychotic patients. 148, 484-488.

Twenty patients with mood-incongruent psychoses and 6 controls were compared on cerebrospinal fluid neurotensin levels, with no significant findings. Significant subsidiary analyses would not survive the Bonferroni correction for multiple comparisons. This is a repeated pattern in fishing expeditions with negative findings in the primary analysis: the authors then conduct numerous sub-analyses and discuss a handful of statistically significant findings at length without correcting for chance.

Christenson, G. A., MacKenzie, T. B., Mitchell, J. E., & Callies,

A. L. (1991). A placebo-controlled double-blind crossover study of fluoxetine in trichotillomania. 148, 1566-1571.

Fluoxetine (Prozac) was found to be no more effective than placebo in treatment of chronic hair pulling. The discussion section is 215 lines long.

McNeil, T. F., Blennow, G., & Lundberg, L. (1992). Congenital malformations and structural developmental anomalies in groups at high risk for psychosis. 149, 57-61.

The authors compared the rates of congenital malformations in the offspring of 84 women with histories of nonorganic psychosis, and those of 100 control women, and found no significant differences between groups. Yet, in their abstract, the authors state: "The inferred genetic risk for psychosis does not appear to be associated with greater rates of early somatic developmental anomalies, suggesting that early developmental anomalies do not represent an expression of genetic influence toward psychosis." This is a good example of how negative findings do not inhibit reductionist editorializing or the faith in a genetic predisposition to psychosis.

In their final paragraph, the authors reiterate their belief in an established genetic risk for psychosis: "[T]he findings appear more to suggest that there is no relation between greater genetic risk and the occurrence of congenital malformations." A parsimonious explanation of the negative finding is that the study has no bearing on whether there is a genetic factor in schizophrenia.

Nothen, M. M., Erdman, J., Korner, J., Lanczik, M., Fritze, J., Fimmers, R., Grandy, D. K., O'Dowd, B., & Propping, P. (1992). Lack of association between dopamine D1 and D2 receptor genes and bipolar affective disorder. 149, 199-201.

This paper is one of five biological fishing expeditions (out of 16 papers in the issue) with no significant findings, in the February 1992 issue of the *Journal*. The authors tested 56 bipolar patients and 69 controls for restriction fragment length polymorphism alleles at the D1 and D2 receptor loci, and found no differences between the two groups.

Simeon, D., Stanley, B., Frances, A., Mann, J. J., Winchel, R., & Stanley, M. (1992). *Self-mutilation in personality disorders: Psychological and biological correlates*. 149, 221-226.

This is a negative fishing expedition disguised with spurious statistically significant findings. The authors measured cerebrospinal fluid 5-HIAA levels and platelet imipramine binding and affinity sites in 26 self-mutilators and 26 controls. The two groups did not differ on CSF 5-HIAA, number of platelet imipramine binding sites, or imipramine affinity. The positive finding was two significant correlations, between number of platelet imipramine receptor sites and self-mutilation and impulsivity, in the self-mutilator group but not the controls, at $p < .05$, out of 15 correlations reported. 5-HIAA levels did not correlate significantly with any clinical variable in either group, yet the authors concluded in their abstract that their results “provide preliminary support for the hypothesis of underlying serotonergic dysfunction facilitating self-mutilation.”

Garber, H.J., & Rivto, E. R. (1992). *Magnetic resonance imaging of the posterior fossa in autistic adults*. 149, 245-247.

Twelve autistic adults and 12 controls were compared on MRI scans of a number of different brain regions, with no differences between groups.

Kumar, A., Yousem, D., Souder, E., Miller, D., Gotlieb, G., Gur, R., & Alavi, A. (1992). *High-intensity signals in Alzheimer's disease without cerebrovascular risk factors: A magnetic resonance imaging evaluation*. 149, 248-250.

There were no differences between 16 Alzheimer's patients and 23 controls on MRI brain scan.

Pomara, N., Singh, R., Deptula, D., Chu, J. C.-Y., Schwartz, M. B., & LeWitt, P.A. (1992). *Glutamate and other CSF amino acids in Alzheimer's disease*. 149, 251-254.

The authors measured the levels of 20 amino acids in the cerebrospinal fluid of 10 Alzheimer's patients and 10 controls. There were five significant differences out of 20 comparisons at $p < .05$, but two showed higher levels in the Alzheimer's group, and three showed lower. None of these findings was significant with the Bonferroni correction applied, which the authors failed to do. They ignored the three amino acids that were lower in the Alzheimer's group, and stated in their abstract: “The authors speculate that the excitotoxic effects of glutamate may contribute to progressive neuronal loss in Alzheimer's disease.”

Gorman, J. M., Warne, P. A., Begg, M. D., Cooper, T. B., Novacenko, H., Williams, J. B., Rabkin, J., Stern, Y., & Ehrhardt, A. A. (1992). *Serum prolactin levels in homosexual and bisexual men with HIV infection*. 149, 367-370.

The authors compared 121 HIV-positive and 79 HIV-negative men on serum prolactin levels with no significant findings.

Wang, Z. W., Crowe, R.R., & Noyes, R. (1992). *Adrenergic receptor genes as candidate genes for panic disorder: A linkage study*. 149, 470-474.

Various adrenergic receptor loci were studied in 14 panic disorder pedigrees with no significant results. Because this was a genetic link-age study, the authors could conceptualize it as an important exclusion study: this conceptualization, of course, requires the prior assumption that panic disorder is inherited.

Brown, F. W., Lewine, R. J., Hudgins, P.A., & Risch, S. C. (1992). *White matter hyperintensity signals in psychiatric and nonpsychiatric subjects*. 149, 620-625.

Brain MRI scans of 229 psychiatric patients and 154 controls yielded no significant findings.

Zilbovicius, M., Garreau, B., Tzourio, N., Mazoyer, B., Bruck, B., Martinot, J.-L., Raynaud, C., Samson, Y., Sy rota, A., & Lelord, G. (1992). *Regional cerebral blood flow in childhood autism: A SPECT study*. 149, 924-930.

Brain scans of 21 autistic children and 14 controls showed no significant findings. The study had 10 authors and 35 subjects.

Geraciotti, T. D., Liddle, R. A., Altemus, M., Demitrack, M.A., & Gold, P. W. (1992). *Regulation of appetite and cholecystokinin secretion in anorexia nervosa*. 149, 958-961.

Six patients and 6 controls showed no significant differences on plasma cholecystokinin levels.

Birmaher, B., Dahl, R. E., Ryan, N. D., Rabinovich, H., Ambrosini, P., Al-Shabbout, M., Novacenko, H., Nelson, B., & Puig-Antich, J. (1992). The dexamethasone suppression test in adolescent outpatients with major depressive disorder. 149, 1040-1045.

The DST was given to 44 depressed and 38 control adolescents with no significant differences between groups.

Gelertner, J., Kennedy, J. L., Grandy, D. K., Zhou, Q.-Y., Civelli, O., Pauls, D. L., Pakstis, A., Kurian, R., Sunahara, R. K., Niznik, H. B., O'Dowd, B., Seeman, P., & Kidd, K. K. (1993). Exclusion of close linkage of Tourette's syndrome to D1 dopamine receptor. 150, 449-453.

The authors established that Tourette's syndrome is not linked to the D1 receptor gene. In the abstract the authors stated: "This exclusion extends the authors' earlier work with the dopamine system in Tourette's syndrome to exclude the two best characterized dopamine receptors from linkage with Tourette's syndrome."

Gorman, J. M., Papp, L. A., Coplan, J., Martinez, J., Liebowitz, M. R., & Klein, D. F. (1993). The effect of acetazolamide on ventilation in panic disorder patients. 150, 1480-1484.

The authors replicated a previous finding that acetazolamide has no effect on panic patients.

Kertzner, R. M., Goetz, R., Todak, G., Cooper, T., Lin, S.-H., Reddy, M. M., Novacenko, H., Williams, J. B., Ehrhardt, A. A., & Gorman, J. M. (1993). Cortisol levels, immune status, and mood in homosexual men with and without HIV infection. 150, 1674-1678.

The authors found no differences between HIV-positive and HIV-negative subjects.

Statistically Significant Findings Of Doubtful Clinical Significance

In many biological papers, there are statistically significant findings, but the magnitude of the differences is of doubtful clinical or biological meaning. Irrelevant statistically significant results are often reported when they do not support the study hypothesis, and when there were no significant findings concerning the key study variables. Considerable effort is often expended to disguise the fact that the results have no real meaning by hiding things in sections on methods or results, not mentioning them in the discussion, creating statistical artifacts, or glossing over the negative findings.

All of this is evidence of ideology driving the field, rather than disinterested curiosity. The effort is to support the cognitive errors analyzed in the previous chapter, not to understand nature. Many of these papers could be characterized as biological fishing expeditions with significant findings.

Denicoff, K. D., Joffe, R., Lakshmanan, M. C., Robbins, J., & Rubinow, D. R. (1990). Neuropsychiatric manifestations of altered thyroid state. 147, 94-99.

As stated in the abstract: "The authors assessed the mood and cognitive effects of sequential T4, T3, and withdrawal of thyroid replacement on 25 patients who had had thyroidectomies for cancer." T3 and T4 are two different forms of thyroid hormone. The problem with the study is imbedded in the tables but not discussed. The main measure of depressed mood used was the Beck Depression Inventory (BDI). To be clinically depressed and enrolled in a drug study, one should usually score above 20 on the BDI, and one will be counted as a drug responder if the score drops to 10 by study end.

The Beck scores of the 25 subjects when not on thyroid replacement averaged 10.14 (S.D. 8.78), compared to 5.50 (S.D. 6.40) on T4 and 5.42 (S.D. 5.53) on T3. An ANOVA on these figures was significant ($F = 12.14$; $df = 2.36$; $p < .01$). The problem is that scores of 5 and 10 are not meaningfully different clinically. Out of 25 patients, only 2 had BDI scores above 20 when not on thyroid replacement, and only 2 experienced BDI score increases of greater than 10 when taken off one of the two forms of thyroid hormone.

It is doubtful that blind independent clinicians could correctly assign these subjects to on-thyroid or not-on-thyroid replacement groups at a level above chance, based on assessment of depression symptoms alone. The depressive response to low thyroid hormone levels should be one of the most robust and clinically meaningful findings in all of biological psychiatry, but it is in fact very weak.

Another problem with this study is that BDI scores reported to one decimal place, let alone two, are meaningless, because the precision of the BDI does not permit such fine discrimination.

Gillin, J. C., Smith, T. L., Irwin, M., Kripke, D. F., Brown, S., & Shuck it, M. (1990). Short REM latency in primary alcoholic patients with secondary depression. 147, 106-109.

This study looks good on first glance, but closer inspection reveals a serious problem. The study was done in a sleep laboratory with sleep EEGs performed on alcoholics with secondary depressions ($N = 12$), alcoholics without secondary depressions ($N = 21$), and controls ($N = 31$). The Bonferroni correction for multiple comparisons was used, but it was applied in a fashion that made insignificant results appear significant. Significance was set at $p < .05$ and Newman-Keuls tests were done on the dependent variables for the three groups. In the table, 34 variables were presented, which means that the corrected significance level should be $p < .0015$. There would then be only one significant difference between groups, which is in the total amount of non-REM sleep.

Instead, the authors applied the Bonferroni correction “on 23 sleep measures on which analyses of variance were performed,” which could be regarded as reasonable, given that the other variables in the table are demographic or clinical. This would yield a corrected significance level of $p < .0022$. Using this significance level, the total amount of sleep time (REM plus non-REM) also becomes significant at $p < .002$. However, these results are meaningless, so the authors salvaged significance for the variables they wanted to differ between groups by limiting the Bonferroni correction to only “the five sleep measures of particular interest.” Now significance was set at $p < .01$, and the key variable of short REM latency, which ties into sleep findings in the depression literature, became significant.

However, REM latency itself was still not significant ($p < .02$), so the authors constructed a variable they called corrected REM latency, which just made significance at $p < .01$. Corrected REM latency is calculated by subtracting the intervening awake time from the REM latency. For those unfamiliar with sleep physiology, REM latency is the period of time between falling asleep and the onset of the first period of REM sleep, and is shorter than normal in clinically depressed patients.

To get statistical significance, the authors of this study had to pull a statistical sleight of hand with the Bonferroni correction and then create a dummy variable. Yet they titled their paper *Short REM Latency in Primary Alcoholic Patients with Secondary Depression* and opened their discussion with these sentences: “These results are consistent with the concept that short REM latency is a biological state marker associated with formally diagnosed (i.e., by DSM-III criteria) depression, secondary as well as primary or endogenous. It should be noted that REM latency was not correlated with scores on the Hamilton depression scale.”

Coffey, C. E., Figiel, G. S., Djang, W. T., & Weiner, R. D. (1990). *Subcortical hyperintensity on magnetic resonance imaging: A comparison of normal and depressed elderly subjects*. 147, 187-189.

In this study, MRI scans were done on 35 depressed elderly patients referred for ECT with no neurological history, 16 depressed elderly patients referred for ECT who had histories of neurological problems, and 22 controls. The authors did this study because “the significance of subcortical hyperintensity in patients with depression remains unclear.” They wanted to control for the effect of neurological problems, which was a good idea. They found significant differences between the group of depressed with no neurological history and the controls, on number of subjects with grade 2 or grade 3 MRI changes (chi square = 4.9, $df = 1$, $p < .03$). However, they excluded subjects with grade 1 changes from the analysis, although these are reported in the table. Of the controls, 77% showed grade 1 periventricular hyperintensity, compared to 43% of the non-neurological subjects and 25% of the neurological subjects; 64% of controls showed grade 1 deep white matter hyperintensity, compared to 37% of the non-neurological subjects and 19% of the neurological subjects. This is the reverse of the pattern for grade 2 and grade 3 changes.

The explanation for exclusion of grade 1 subjects was: “On the basis of the reported occurrence and severity of subcortical hyperintensity in normal elderly subjects, we hypothesized that grade 2 and grade 3 periventricular and deep white matter hyperintensity would be more common in our depressed inpatients than in the control group.” Did they really mean that failure to exclude grade 1 changes would introduce too much noise and threaten significance? The decision to exclude grade 1 subjects makes both the findings and the methodology questionable.

Karasjgi, B., Rifkin, A., Doddi, S., & Kolli, R. (1990). *The prevalence of anxiety disorders in patients with chronic obstructive pulmonary disease*. 147, 200-201.

The authors interviewed 50 subjects with chronic obstructive pulmonary disease and found a lifetime prevalence of anxiety disorders of 16%, compared to 15% in the general population. They observed that 8% of their subjects had panic disorder, however, compared to 1.5% of the general population, which they considered to be significant, although they did not do a statistical test such as a z score to determine whether this was actually significant. They also noted a lifetime prevalence of mood disorders of 18% in their sample, but did not return to this at all in the discussion section. Nor did they point out the reciprocal of their finding concerning panic disorder—namely, that 7% of their sample had non-panic anxiety disorders compared to 13.5% of the general population. Finally, they did not say anything about the age at onset of the panic disorder in their subjects which, given the natural history of panic disorder and obstructive lung disease, was probably 20 to 30 years before the onset of pulmonary symptoms (the mean age of their subjects was 64.96 years, S.D. 9.70).

If age-at-onset data were included, the findings would be that obstructive lung disease has an onset decades later than mood and anxiety disorders; that the rate of mood and anxiety disorders is equal in their sample and no different from the general population; and that a future history of lung disease protects against the onset of non-panic anxiety disorders occurring decades earlier. These are meaningless findings. The authors, as could be predicted from the title of their paper, discuss bioreductionist theories of panic focused on the locus ceruleus, and try to connect the physiology of chronic obstructive pulmonary disease to that of panic disorder.

Siever, L. J., Keefe, R., Bernstein, D. P., Coccaro, E. F., Klar, H. M., Zemishlany, Z., Peterson, A. E., Davidson, M., Mahon, T., & Mohs, R. (1990). *Eye tracking impairment in clinically identified patients with schizotypal personality disorder*. 147, 740-745.

The authors of this paper concluded from their data: “[O]ur results are the first to demonstrate impaired tracking in clinically identified schizotypal patients and thus support the hypothesis that schizotypal personality disorder, as diagnosed in clinical settings, may be considered a schizophrenia-related disorder.” Abnormalities of eye tracking have been shown to correlate with schizophrenia in previous research, which I am not disputing. The problem here is with differential reporting of statistical analyses to support the bioreductionist concept of the schizophrenia spectrum.

The authors measured smooth eye pursuit movement in 26 subjects with clinically diagnosed schizotypal personality disorder, 17 with other personality disorders, 44 with schizophrenia, and 29 controls. They did not address the problem of the low interrater reliability of even the most rigorous structured-interview Axis II diagnoses, which is crucial for their research. They did report the rates of other personality disorders in their two key groups, however, which were as follows:

	ScSchizotypal Group: Percent Positive	Other Personality Disorder Group: Percent Positive
Paranoid	53.8	
Borderline	38.5	52.9
Histrionic	23.1	41.2
Avoidant	23.1	11.8
Antisocial	19.2	5.9
Compulsive	19.2	47.1
Schizoid	7.7	
Dependent	3.8	11.8
Mixed		17.7
Narcissistic		17.7
Passive-Aggressive		5.9

The authors did not report whether there were any significant differences between the two groups on the rates of any of these other personality disorders; to do so would have called their conclusions into question. It is obvious by visual inspection that chi-square analyses would reveal no significant difference in the frequency of many of the personality disorders in the two groups. Like the extensive over-all Axis II comorbidity of both groups, this is a crucial limitation of their study.

In their analyses of the eye-tracking findings, the authors pointed out that the schizotypal and schizophrenia groups both differed from normal controls, but the other personality disorder group did not. However, they strategically failed to report the result of comparing the schizotypal and schizophrenic groups to the other personality disorder group, which is nonsignificant, saying only that “mean qualitative ratings for the patients with other personality disorders were intermediate between those of the schizotypal and normal control cohorts.” The data are as follows:

	<u>Eye Tracking Value</u>	
	Mean	S.D.
Schizotypal	2.9	0.8
Other personality	2.6	0.7
Schizophrenia	3.0	0.9
Control	2.1	0.6

The data show that there is no significant difference among the three clinical groups; therefore one could as easily conclude, logically, that schizophrenia is a personality disorder. Instead, the authors reach a reductionist conclusion:

The finding of impaired tracking in schizotypal patients is consistent with evidence from other studies suggesting that schizotypal personality disorder may be related to schizophrenia with respect to its genetics, biology, treatment response, and outcome. The refinement of biological measures with a substantial genetic basis such as eye tracking in schizotypal patients and control subjects thus may enhance resolution of selection of affected phenotypes in molecular genetic linkage studies of schizophrenia, as well as advance our knowledge of the pathophysiology of the schizophrenia-related disorders.

It is remarkable how many of the cognitive errors analyzed in the previous chapter are packed into these two sentences.

Southwick, S. M., Yehuda, R., Giller, E. L., & Perry, B. D. (1990). *Altered platelet alpha-2-adrenergic receptor binding sites in borderline personality disorder*. 147, 1014-1017.

In this study, 13 nonmedicated borderlines, 11 borderlines medicated with benzodiazepines, and 18 controls were assayed for platelet alpha-2-adrenergic binding sites. The anxiety subscale scores on the Hamilton Depression Scale (HAM-O) of the two borderline groups did not differ. The finding was that the nonmedicated border lines had fewer receptors than the other two groups, which the authors speculated might be due to down-regulation of receptors by the greater catecholamine release occurring in the nonmedicated borderlines. This doesn't make any sense. The effect should occur only if the nonmedicated group is more anxious and therefore releasing more catecholamines. The data are in the opposite direction of the conclusion.

To support their conclusion, the authors did correlational analyses separately in the two borderline groups, and found that there was a significant correlation between HAM-D anxiety sub-score and receptor density at one of 2 sites where assays were done, but no significant correlation at either site in the medicated group. This is an artifact that is overridden by the lack of difference in anxiety between the two groups.

Walker, E., & Lewine, R. J. (1990). *Prediction of adult-onset schizophrenia from childhood home movies of the patients*. 147, 1052-1056.

This is an interesting study in which blind raters tried to predict adult schizophrenia from watching home movies from childhood of schizophrenic patients and their siblings. In the analysis used by the authors, they obtained significant diagnostic hit rates for 1 sibship on 2 out of 4 film segments, and on 1 sibship on 1 out of 2 segments. There were 4 patients and 5 unaffected siblings; films of 2 siblings were reviewed for 1 patient. Four different segments at different ages were reviewed for each of 3 patients, and 2 segments for the patient with 2 siblings. Altogether, 302 judgments of schizophrenic versus non-schizophrenic were made by the varying numbers of independent raters for each sibship.

Out of these 302 judgments, there were 84 true positive, 45 false positive, 111 true negative, and 58 false negative diagnoses made (I had to calculate these figures from the table; they were not given). This means that the overall rate of agreement between adult clinical diagnosis and diagnosis by childhood home movies was $195/302 = 65\%$. Applying Cohen's kappa to this result yields an interrater reliability of $\kappa = 0.30$, which is not clinically significant. This paper is included in this section because the findings are of doubtful clinical significance using the authors' analyses, and of no significance when overall hit rate corrected for chance is calculated.

Breier, A., Wolkowitz, O. M., Roy, A., Potter, W., & Pickar, D. (1990). *Plasma norepinephrine in chronic schizophrenia*. 147, 1467-1470.

This study involves measurement of plasma and cerebrospinal fluid (CSF) norepinephrine levels resting and standing in 14 schizophrenics and 33 controls. A variety of positive results are presented but they obscure the core finding, which is no difference between the two groups on CSF levels. The significant findings were limited to plasma and correlations between CSF and plasma levels. The plasma levels have nothing to do with the brain or any possible brain pathology in schizophrenia.

Yet, undaunted, the authors concluded: "Thus, it is possible that the above-normal peripheral sympathetic nervous system activity found in this and other studies of schizophrenia reflects altered central processes involving dopaminergic and noradrenergic function."

Spivak, B., Radwan, M., Brandon, J., Molcho, A., Ohring, R., Tyano, S., & Weizman, A. (1991). *Cold agglutinin autoantibodies in psychiatric patients: Their relation to diagnosis and pharmacological treatment*. 148, 244-247.

The authors measured cold agglutinin titers, which are indirect indicators of infection and autoimmune activity, in 90 schizophrenics, 54 bipolar patients, and 22 subjects with depression. They found positive titers in 42.4% of the schizophrenics, 11.1% of the bipolars, and 8.1% of the depressives, which was statistically significant. They noted, however, that, "titers up to 1:4, such as were found in our patients, are not considered to be evidence of pathology, and can be found in healthy populations too." Their finding had no biological meaning.

Yehuda, R., Lowy, M. T., Southwick, S. M., Shaffer, D., & Giller,

E. L. (1991). *Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder*. 148, 499-504.

In this study, 15 Vietnam vets with posttraumatic stress disorder were compared to 11 controls on serum cortisol levels alone, correlation of cortisol levels with glucocorticoid receptor densities, and receptor densities alone. The only significant finding was in number of receptors, but given the lack of differences on the other two measures, this finding is of dubious biological significance.

Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R., Dewey, S., Bendriem, B., Alpert, R., & Hoff, A. (1991). *Changes in brain glucose metabolism in cocaine dependence and withdrawal*.

148, 621-626.

The authors measured brain metabolism in cocaine addicts at 1 week and again at 2 to 4 weeks post-withdrawal using PET scans. There were 17 addicts and 15 controls. The two groups differed significantly only at week one. Although this is interesting, it must be attributed to bio-logically nonspecific characteristics of the withdrawal state pending further research, which must include withdrawal from various substances. Additionally, the finding of increased activity in the orbito-frontal cortex and basal ganglia, noted during week one of cocaine withdrawal, has also been observed in obsessive-compulsive disorder, according to the authors. This fact completely erodes any biological specificity to the finding in the cocaine addicts.

Lewine, R. J., Risch, S. C., Risby, E., Stipetic, M., Jewart, D., Eccard, M., Caudle, J., & Pollard, W. (1991). *Lateral ventricle-brain ratio and balance between CSF HVA and 5-HIAA in schizophrenia*. 148, 1189-1194.

The authors compared 45 patients with schizophrenia, 28 with mood disorders, and 91 controls on ventricle-brain ratio (VBR), HVA, and 5-HIAA, with no significant findings. In a subsidiary analysis, they found that the ratio of HVA to 5-HIAA was significantly correlated with VBR, however, and they were able to construct reasons for this being a publishable finding, despite its questionable biological meaning.

Siever, L. J., Amin, F., Coccaro, E. F., Bernstein, D., Kavoussi, R. J., Kalus, O., Horvath, T. B., Warne, P., Davidson, M., & Davis, K. L. (1991). *Plasma homovanillic acid in schizotypal personality disorder*. 148, 1246-1248.

The authors measured plasma HVA, which has no consistent relationship with psychiatrically significant levels of HVA in the brain, in 11 subjects with schizotypal personality disorder, 7 with other personality disorders, and 6 controls. They found that the schizotypal group differed from the controls, and concluded: "These findings suggest dopaminergic mechanisms underlying the psychotic-like symptoms of schizotypal personality disorder and support the concept that the psychotic-like symptoms of schizotypal personality disorder and psychotic symptoms of schizophrenia are not only phenomenologically similar but are biologically related as well."

The problem with the study is that the other personality disorder group did not differ from either the schizotypal group or the controls. HVA levels were: schizotypal 12.9 (S.D., 4.60); other personality disorders 9.1 (S.D., 2.53); and controls 7.8 (S.D., 1.30). This pattern was observed in other studies published over the four-year period. One could as well conclude that symptoms of other personality disorders are bio-logically normal, or alternatively, that they are related to the biology of schizophrenia. For the authors' conclusions to make sense, the other personality disorder group *must* be no different from controls and significantly different from schizotypals. Those not familiar with DSM-IV criteria might be alarmed to know that the symptoms of biologically driven schizophrenia-spectrum brain illness listed in DSM-IV under criteria for schizotypal personality disorder include "odd beliefs or magical thinking that influence behavior and are inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense."

This study had 24 subjects and 10 authors.

Cartwright, R. D., Kravitz, H. M., Eastman, C., & Wood, E. (1991). *REM latency and the recovery from depression: Getting over divorce*. 148, 1530-1535.

The authors measured REM latency in 100 subjects who were undergoing marital separation; of these, 70 were clinically depressed. The study was interesting and well done, but the finding directly contradicts all previous biological thinking about the significance of shortened REM latency in depression, a replicated and consistent finding. Shortened REM latency is supposed to tap into the diagnostically specific biology of depression. The problem is that, in this study, shortened REM latency predicted a better outcome at one-year follow-up. This author concluded: "Depressed individuals with normal REM latencies may need more aggressive treatment interventions." According to this logic, being biologically normal is a sign of being psychiatrically sicker.

Bajwa, W. K., Asnis, G. M., Sanderson, W. C., Iran, A., & van Praag, H. M. (1992). High cholesterol levels in patients with panic disorder. 149, 376-378.

The authors compared cholesterol levels in 30 patients with panic disorder, 30 with depression, and 30 controls. The cholesterol levels of the panic patients were significantly higher: mean of 224.7 (S.D., 43.5) compared to 189.8 (S.D., 32.8) for depression and 183.6 (S.D., 37.7) for controls ($F = 10.10$; $df = 2, 87$; $p < .001$), but “the cholesterol levels of the patients with panic disorder as a group remained within the normal range (150-250 mg/dl). In addition, we did not measure high-density lipoprotein (HDL) or low-density lipoprotein (LDL) cholesterol levels, which are considered to be more specifically correlated with risk of coronary artery disease.”

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Hershey, T., Johnson, J. C., & Bunney, W. E. (1992). Effect of sleep deprivation on brain metabolism of depressed patients. 149, 538-543.

The authors did PET scans on 15 depressed patients and 15 controls. There were 18 comparisons, and no findings would survive the Bonferroni correction. This paper is noteworthy because in the main table the authors reported that, for some brain regions, the sleep-deprivation responders had a higher baseline metabolic rate than the non-responders; of these comparisons, they noted that the finding was not significant after application of the Bonferroni correction for only one comparison, when that was true for all data in the study. This is an example of selective application of the Bonferroni correction within a single table, which violates the most elementary rules of scientific research. The Bonferroni correction was perhaps not applied to the cingulate findings in this study because: “In a previous study [by the same group], the cingulate gyms was the only cortical structure with a significantly higher glucose metabolic rate during REM sleep than during the normal waking state.”

Williamson, P., Pelz, D., Merskey, H., Morrison, S., Karlik, S., Drost, D., Carr, T., & Conlon, P. (1992). Frontal, temporal, and striatal proton relaxation times in schizophrenic patients and normal comparison subjects. 149, 549-551.

This is a good study with no methodological problems or reductionist editorializing. MRI values in a specific brain region were significantly different, in a comparison of 10 schizophrenics and 10 controls. I include it because, in the footnotes to the table, each of 5 statistical foot-notes states that the findings were significant after correction for multiple comparisons. This paper appeared in the same issue as the previous paper, therefore this quality of methodology should have been demanded of the Wu et al. (1992) paper as well.

Lydiard, R. B., Ballenger, J. C., Laraia, M. T., Fossey, M. D., & Beinfeld, M. C. (1992). CSF cholecystokinin concentrations in patients with panic disorder and in normal comparison subjects. 149, 691-693.

CSF cholecystokinin levels were compared in 25 panic patients and 16 controls. The findings were statistically significant but the difference in absolute values and the size of the t statistic make the findings of doubtful biological significance. The patients had a mean value of 20.6 (S.D., 7.7) and the controls 16.2 (S.D., 5.9) ($t = 2.05$, $df = 39$, $p < .05$).

Petitto, J. M., Folds, J. D., Ozer, H., Quade, D., & Evans, D. L. (1992). Abnormal diurnal variation in circulating natural killer cell phenotypes and cytotoxic activity in major depression. 149, 694-696.

The authors measured immunological variables in 24 depressed patients and 24 controls. They studied two immunological cell markers, Leu-7 and Leu-11, and found more diurnal variation in cell activity in normals than in patients for one type of cell, but not for the other. They could not account for the difference between cell types and did not comment on the biological meaning of their finding.

Luchins, D. J., Cohen, D., Hanrahan, P., Eisdorfer, C., Pavexa, G., Ashford, J. W., Gorelick, P., Hirschman, R., Freels, S., Levy, P., Semla, T., & Shaw, H. (1992). Are there clinical differences between familial and nonfamilial Alzheimer's disease? 149, 1023-1027.

This study is of doubtful clinical significance because of the poor performance of clinicians in predicting Alzheimer's, as discussed below, and because the Alzheimer's disease of the relatives was “reported” in an unspecified fashion. The two groups, supposed familial and non-familial Alzheimer's, did not differ on numerous variables.

Coryell, W., & Tsuang, D. (1992). Hypothalamic-pituitary-adrenal axis hyperactivity and psychosis: Recovery during an 8-year followup. 149, 1033-1039.

This study is remarkable because of its finding that biologically normal patients have a poorer clinical outcome than those with an abnormal dexamethasone suppression test. This finding is the exact opposite of that predicted by bioreductionist psychiatry.

Cleghorn, J. M., Franco, S., Szechtman, B., Kaplan, R. D., Szechtman, H., Brown, G., Nahmias, C., & Garnett, E. S. (1992). Toward a brain map of auditory hallucinations. 149, 1062-1069.

There were many comparisons and many significant findings in this PET scan study, but none would survive the Bonferroni correction for multiple comparisons.

Schwartz, J. M., Aylward, E., Barta, P. E., Tune, L. E., & Pearlson, G.D. (1992). Sylvian fissure size in schizophrenia measured with the magnetic resonance imaging rating protocol of the consortium to establish a registry for Alzheimer's disease. 149, 1195-1198.

Various brain areas were measured using MRI scans in 48 schizophrenics and 51 controls, with a specific finding that the only difference was that the schizophrenics had wider sylvian fissures. This finding is of potential interest because it implies tissue loss in the temporal lobes, which could be related to the cause of schizophrenia. However, the sylvian fissure was measured on a scale that goes from zero, for no atrophy, to 3.0 for severe atrophy, and no schizophrenics scored above 1.0, meaning that the range of variation may have been biologically trivial. The table in the paper looks like this:

Rating of Sylvian Fissure Atrophy	Number of Subjects	
	Schizophrenic (N = 48)	Normal (N = 51)
Right 0.0	19	38
0.5	25	13
1.0	4	0
Left 0.0	30	46
0.5	18	5

This does not present a robust, meaningful biological finding. The kappa for interrater reliability on reading the scans was modest (only

“0.60 or greater”), making the biological significance of these fine differences even more doubtful.

Peselow, E. D., Sanfilipo, M. P., Difiglia, C., & Fieve, R. R. (1992). Melancholic/endogenous depression and response to somatic treatment and placebo. 149, 1324-1334.

A total of 231 patients entered into drug trials for depression were analyzed for response to placebo and medication. The data showed: “Moderately depressed patients with DSM-III melancholia had a significantly better response to active medication than did severely de-pressed patients with melancholia and showed the greatest difference between active medication and response to placebo.” Yet, given that this finding contradicts the reductionist assumption that more severe illness means more severe biological abnormalities and greater need for medication, the authors concluded: “This finding suggests that patients who have DSM-III melancholia may be unresponsive to non-somatic treatments.” One could just as easily conclude that the more severe the depression, the less biological it is, and therefore the less responsive to medication.

The data are twisted in their interpretation, because the moderately depressed patients with melancholia had a complete response rate to medication of 38.2% and to placebo of 5.0%; the severely depressed patients with melancholia had a complete response rate to medication of 14.3% and to placebo of 4.2%. The greater gap between medication and placebo is an artifact of the result that the severe patients had a lower response rate to medication while placebo response rates were equal, which supports a conclusion that more severe illness does not affect the placebo response rate but reduces the efficacy of medication.

In examining the rates of partial response of the two groups, one finds that the moderate group had a medication response rate of 35.3% and placebo response rate of 25.0%; the severe group had a medication response rate of 23.8% and placebo response rate of 12.5%. If one were to base conclusions on rates of partial response, the gap between drug and placebo response rates would be equal for the two groups, which is not consistent with the authors' conclusions. Close examination of the table in which these data appear shows an erratic, inconsistent pattern when placebo and drug responses are rated as complete or partial and when severe and moderate patients with and without melancholia are compared. For instance, moderately depressed patients without melancholia have the same gap between drug and placebo responses as severely de-pressed patients with melancholia (11.0 and 10.1, respectively).

The data do not support any consistent conclusions, and there are no significant findings when the Bonferroni correction is applied.

Andreasson, P. J., Altemus, M., Zametkin, King, A. C., Lucinio, J., & Cohen, R. M. (1992). *Regional cerebral glucose metabolism in bulimia nervosa*. 149, 1506-1513.

PET scans were done in 11 bulimics and 11 controls. The main table in the paper gives 51 comparisons of the two groups, of which 5 are significant at $p < .05$, but none of which would survive the Bonferroni correction. In Table 2, there are 9 comparisons, of which none is significant at $p < .05$; in Table 3, all 8 comparisons are significant at $p < .05$. Table 3 also deals with degree of asymmetry between hemispheres, which was greater in 5 brain regions for bulimics and 3 for controls. These simply are not robust findings.

Buchanan, R. W., Breier, A., Kirkpatrick, B., Elkashef, A., Munson, R. C., Gellad, F., & Carpenter, W. T. (1993). *Structural abnormalities in deficit and nondeficit schizophrenia*. 150, 59-65.

The authors did MRI scans on 17 deficit-symptom schizophrenics, 24 nondeficit schizophrenics, and 30 normal controls. Total brain volume did not differ among the three groups; there were scattered, inconsistent differences among the groups on degree of volume asymmetry between hemispheres for certain brain regions. None of these would survive correction for multiple comparisons.

Yehuda, R., Southwick, S. M., Krystal, J. H., Bremner, D., Charney, D. S., & Mason, J. W. (1993). *Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder*. 150, 83-86.

In this study, 21 subjects with posttraumatic stress disorder and 12 controls were given the DST. The paradoxical finding was that the PTSD patients were more biologically normal than the controls. Using a cutoff of 5 ug/ dl, 5 out of 12 controls were DST non-suppressors at both 8:00 AM. and 4 P.M., a very unusual finding of high significance. The rate of non-suppression in controls should be 5%. The so-called positive finding about PTSD is an artifact of using a highly abnormal control group.

Andreassen, N. C., Flaum, M., Swayze, V., O'Leary, D. S., Alliger, R., Cohen, G., Ehrhardt, J., & Yuh, W. T. C. (1993). *Intelligence and brain structure in normal individuals*. 150, 130-134.

The authors did MRI scans and IQ tests in 67 normal volunteers. Table 3 includes 72 correlation coefficients, none of which would be significant with the Bonferroni correction. The authors could not advance any specific hypotheses as to why males and females differed on many values.

Volkow, N. D., Wang, G.-J., Hitzemann, R., Fowler, J. S., Wolf, A. P., Pappas, N., Bigon, A., & Dewey, S. L. (1993).. *Decreased cerebral response to inhibitory neurotransmission in alcoholics*. 150, 417-422.

This study compared PET scans in 10 alcoholics and 12 controls, after they had been given lorazepam. There was no difference between the groups in whole brain metabolic rates, and there would have been no significant differences between the groups in any brain regions if the Bonferroni correction had been applied. The greater reduction in brain metabolism in three brain regions in response to lorazepam among the controls, the key observation of the paper, was an artifact of the lower resting metabolic rate of the alcoholics on placebo.

Altemus, M., Pigott, T., L'Heureux, F., Davis, C. L., Rubinow, D. R., Murphy, D. L., & Gold, P. W. (1993). *CSF somatostatin in obsessive-compulsive disorder*. 150, 460-464.

The authors found higher CSF somatostatin levels in 15 obsessive-compulsive patients than in 27 controls. Values were 58.3 pmol/liter (S.D. 13.8) for patients and 45.8 (S.D. 9.0) for controls ($t = 3.6$, $df = 40$, $p < .001$). However, the authors stated: "The functional importance of the high CSF levels of somatostatin and the positive correlations between CSF somatostatin and CSF, CRH, and CSF arginine vasopressin in patients with obsessive-compulsive disorder remains to be determined."

Haggerty, J. J., Stern, R. A., Mason, G. A., Beckwith, J., Morey, C. E., & Prange, A. J. (1993). *Subclinical hypothyroidism: A modifiable risk factor or depression?* 150, 508-510.

The authors found a lifetime history of depression in 56% of 16 subjects with subclinical hypothyroidism and 2% of 15 controls, a difference significant at $p < .04$. The two groups did not differ on levels of thyroid hormone, but the subclinical hypothyroid group had higher thyroid-stimulating hormone levels. The authors had no data as to whether the depressions occurred prior to or after the onset of the subclinical hypothyroidism, and commented: "It is also conceivable, however, that the association we observed was not due to the effects of subclinical hypothyroidism but rather to the influence of depression on the development of hypothyroidism, mediated perhaps by altered autoimmune processes."

That depression could cause hypothyroidism is highly unlikely, although it is conceivable that a cause of depression could also be a cause of hypothyroidism.

DeBellis, M. D., Gold, P. W., Geraciotti, T. C., Listwak, S. J., & Kling, M. A. (1993). Association of fluoxetine treatment with reductions of CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. 150, 656-657.

There was no correlation between the magnitude of reduction in Hamilton Depression Scale scores and the magnitude of changes in CSF, CRH, or CSF arginine vasopressin in 9 depressed patients, when measurements were taken before and after treatment with fluoxetine. The observed reduction in the biological variables is therefore clinically spurious.

Nunes, E. V., McGrath, P. J., Quitkin, F. M., Stewart, J.P., Harrison, W., Tricamo, E., & Ocepek-Welikson, K. (1993). Imipramine treatment of alcoholism with comorbid depression. 150, 963-965.

In this study, 45% of depressed alcoholics responded to an open trial of imipramine, but this does not differ from the placebo response rate recognized in the literature on depression.

Lydiard, R. B., Brewerton, T. D., Fossey, M. D., Laraia, M. T., Stuart, G., Beinfeld, M. C., & Ballenger, J. C. (1993). CSF cholecystokinin octapeptide in patients with bulimia nervosa and in normal comparison subjects 150,1099-1101.

Brambila, F., Bellodi, L., Perna, G., Barberi, A., Panerai, A., & Sacerdote, P. (1993). Lymphocyte cholecystokinin concentrations in panic disorder. 150, 1111-1113.

I am discussing these two papers together because they appear a few pages apart in the same issue of the *Journal*, and both deal with cholecystokinin octapeptide (CCK-8), although the measurements are done differently. The findings from the two studies concerning CCK levels are:

Bulimia	13.5	S.D. 6.5
Bulimia controls	20.5	S.D. 7.5
Panic disorder	35	S.D. 21
Panic controls	58	S.D. 32

The same finding in two unrelated disorders means that the results are of doubtful clinical and biological importance or specificity. One might want to postulate a CCK-spectrum disorder, however, including panic disorder and bulimia, given the logic of biological psychiatry.

Maddock, R. J., Cater, C. S., Magliozzi, J. R., & Gietzen, D. W. E. (1993). Evidence that decreased function of lymphocyte beta adrenoreceptors reflects regulatory and adaptive processes in panic disorder with agoraphobia. 150, 1219-1225.

The basic finding in this study is that increased anxiety leads to down-regulation of beta adrenoreceptors, and treatment with benzodiazepines reduces anxiety and results in up-regulation of receptors. Although this is an acceptable study methodologically, the findings are scientifically banal.

Siegel, B. V., Buchsbaum, M. S., Bunney, W. E., Gottschalk, L. A., Haier, R. J., Lohr, J. B., Lottenberg, S., Najafi, A., Nuechterlein, K. H., Potkin, S. G., & Wu, J. C. (1993). Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. 150, 1325-1336.

The tables in this paper present 101 rows of PET scan data on 70 schizophrenics and 30 controls. Each row has 4 to 6 data points in it. The authors stated:

For exploratory analyses, because of the large number of correlations and t tests calculated, significance levels of $p < .05$ were considered a trend, and $p < .001$ was considered significant. Bonferroni corrections were not re-reported; we believe that using less stringent corrections in a large exploratory study such as this one is useful for comparison to findings of other investigators. Thus, we attempted to reduce the possibilities of Type I errors in three ways: by using repeated measures ANOVA, by labeling some analyses as exploratory and correcting them for multiple comparisons, and by at-attempting to match already published findings.

In this literature, the Bonferroni correction can be used only some of the time in a dataset to avoid the result of no significant findings, a softened informal Bonferroni correction can be used to preserve significance, and insignificant data can be reported so that they can be validated by similar insignificant data from other investigators.

Morgan, M. J., Cascella, N. G., Stapleton, J. M., Phillips, R. L., Yung, B. C. K., Wong, D. F., Shya, E. K., & London, E. D. (1993). Sensitivity to subjective effects of cocaine in drug abusers: Relationship to cerebral ventricle size. 150, 1712-1717.

In this study, the authors correlated ventricle-brain ratios with subjective response to intravenous cocaine in 20 male polydrug users. They stated, in a footnote to Table 1, that the findings are “significant at $p < .05$ without correction for multiple comparisons.” One assumes that, with correction, none would be significant. They also noted that “none of these subjects was considered to show pathological ventriculomegaly when the CT scans were inspected by a radiologist.” The study, then, involves nonsignificant findings within the normal range. The nature of the demand characteristics in the study and the ethics of giving drug addicts I.V. cocaine to study a scientifically weak hypothesis are not discussed.

Twin, Family, And Genetic Studies

Twin and genetic studies strike to the heart of our thesis in this book, so I paid special attention to any such research, looking for conceptual and methodological flaws. I have included here several examples of studies that are well conducted and free of ideological distortion, to demonstrate that my analysis is not based on hostility to this category of research.

Segal, N. L., Dysken, M. W., Bouchard, T. J., Pedersen, N. L., Eckert, E. D., & Heston, L. L. (1990). Tourette's disorder in a set of reared-apart triplets: Genetic and environmental variables. 147, 196-199.

This is a good study and worth publishing, but the question is: What do the findings mean? The methodology is flawless, and the twins actually were reared apart. The pattern in the pedigree is incomprehensible genetically, however. The pedigree chart consists of four generations: in the oldest, two brothers had Tourette's. One of these brothers had no children, and the other married twice. By one wife he had no Tourette's progeny out of 9 relatives (2 children, 4 grandchildren, 3 great-grandchildren). By the other, he had 5 Tourette's progeny out of 10 relatives, including a set of triplets—2 monozygotic girls and a boy—all of whom had Tourette's. One of the girls and the boy each had three unaffected children and no grandchildren. One of the MZ girls had two affected children, a boy and a girl, one unaffected son, and an unaffected grandson by her affected daughter.

The authors concluded: “The presence of Tourette's disorder in an adult monozygotic/dyzygotic set of triplets raised apart from early in-fancy provides unique evidence that genetic factors are important in the development of this disorder. The presence of this disorder among the first-degree relatives of the triplets, both those living together and those living apart, also underlines the importance of genetic effects.” In fact, the data do not differentiate genetic factors from intrauterine trauma. An alternative hypothesis is that there is no genetic component to Tourette's and that two mothers in this pedigree had infections or were exposed to other toxins during pregnancy. The girl with Tourette's in the third generation, whose mother and brother had Tourette's, also had myasthenia gravis, which suggests some diagnostically nonspecific factor at work.

Pearson, G. D., Ross, C. A., Lohr, W. D., Rovner, B. W., Chase, G. A., & Folstein, M. F. (1990). Association between family history of affective disorder and the depressive syndrome of Alzheimer's disease. 147, 452-456.

This paper is useful because it contains a direct statement of the fallacy that if a disorder runs in families, that is evidence of a genetic cause or contribution. It is a study comparing the rate of depression in relatives of 41 depressed Alzheimer's patients to the rate in relatives of 71 non-depressed Alzheimer's patients. The authors state in their abstract: “The depressed patients had significantly more first- and second-degree relatives with depression than did control subjects. The lifetime risk for major depression, adjusted for differences in age distribution, was significantly greater in first-degree relatives of index patients, suggesting that depression in Alzheimer's disease is genetically related to primary affective disorder.”

Klein, D. N. (1990). Symptom criteria and family history in major depression. 147, 850-854.

The author interviewed 82 outpatients with a current major depressive episode but no bipolar history, and 27 outpatients with no affective diagnoses, most of whom had anxiety and personality disorders. All subjects reported on lifetime history of depression in their first-degree relatives via Family History Research Diagnostic Criteria, but no first-degree relatives were interviewed directly.

The study yielded a negative finding: “The rates [of depression] in relatives of neither group differed significantly from the rates in relatives of patients with non-affective disorders. Finally, the rates of bipolar disorder in the relatives of all three groups of probands did not differ significantly.” Why is the author talking about three groups when the study contained only two groups in its original design? This is because of the negative findings. The author divided the depressed group ($N = 82$) into two subgroups in order to

generate significant data: (a) depressed subjects positive for 4 or 5 symptoms, and (b) those positive for 6, 7, or 8 symptoms. Using these subgroups, he was able to generate sufficient findings to produce a publication. This is analogous to creating an affective spectrum or schizophrenia spectrum to create significant findings in genetic studies, when there are negative findings with respect to schizophrenia alone, as analyzed by Dr. Pam in Chapter 1.

Torgersen, S. (1990). *Comorbidity of major depression and anxiety disorders in twin pairs*. 147, 1199-1202.

This is a study of three diagnostic subgroups in a sample of 177 twin pairs: major depression only, major depression with anxiety disorders, and anxiety disorders only. It contains all the flaws of logic analyzed by Dr. Pam in Chapter 1. The author mentions the equal environments problem, but then ignores it in the rest of the paper: "The difference between concordance rates among monozygotic and dizygotic twins might also be due to chance. Furthermore, a higher concordance among monozygotic than dizygotic twins might be a consequence of a more similar environment for monozygotic twin partners than for dizygotic twin partners."

What do the data look like? The author presents two tables, one with anxiety disorders in general, one limited to panic attacks alone. This results in 18 cells in the two tables combined, with a concordance rate for monozygotic and another for dizygotic twins in each cell. Each table lists three proband diagnoses in the vertical column versus three co-twin diagnoses in the horizontal row.

Out of the 18 cells, the frequency of a positive co-twin diagnosis in the monozygotic pairs exceeds that in the dizygotic pairs by 10% only 4 times. Only two of these show what could be called a *breeding true* pattern: anxiety disorder only is more common in co-twins of anxiety disorder only monozygotic probands than in co-twins of dizygotic probands in both tables. In none of the 6 comparisons involving probands with major depression only was there a difference in frequency of depression of 10% between co-twin rates in monozygotic and dizygotic pairs. The data therefore rule out a genetic component to pure depression in this sample and are consistent with, but do not rule in or out, a genetic component to pure anxiety disorder. With application of the Bonferroni correction, there would be no significant findings. The significant findings in the study are typified by an odds ratio of 9.6 for monozygotic co-twins versus dizygotic co-twins of affected probands; however, the 95% confidence interval for this value is 1.1-115.5.

This finding applies to the higher frequency of major depression with anxiety in monozygotic co-twins of probands with major depression only, compared to that in dizygotic twin pairs. The absolute values are an 18.8% frequency in monozygotes and 8.0% in dizygotes, neither of which is notably different from the range of norms in the general population.

Winokur, G., & Coryell, W. (1991). *Familial alcoholism in primary major depressive episode*. 148, 184-188.

This is a good study without intrusion of reductionism.

Biederman, J., Faraone, S. V., Keenan, K., Steingard, R., & Tsuang, M. T. (1991). *Familial association between attention deficit disorder and anxiety disorders*. 148, 251-256.

This is a good paper, except for the cognitive error that *if it runs in families it must be genetic*, which the authors make in their introduction: "Converging evidence implicates a genetic component in anxiety disorders and ADD. In a study of children with anxiety disorders, Last et al. reported that mothers of anxious children had a significantly higher risk for adult and childhood anxiety disorders than mothers of normal children."

Reiss, D., Plomin, R., & Hetherington, E. M. (1991). *Genetics and psychiatry: An unheralded window on the environment*. 148, 283-291.

This paper would make an excellent chapter in the present book, except that the authors have not grasped the seriousness of the methodological limitations to the biogenetic literature on psychiatric disorders. These limitations, once analyzed and understood, lead to the irrefutable conclusion that no genetic component to schizophrenia or bipolar mood disorder has yet been demonstrated. The authors write:

As the research in molecular genetics has gathered momentum, it has partially broken loose from its original moorings. The search for specific genes in unipolar, bipolar, and schizophrenic illness began with the demonstration of significant genetic effects, but not exclusive genetic effects, for both disorders. That is, bipolar and related illnesses occurred among family members of probands with these illnesses more frequently than in the general population, concordances were generally higher in monozygotic twins than in dizygotic twins, and, in studies with the most rigorous designs, the frequency of the illness was higher in biological than in adopted relatives.

The same patterns hold for schizophrenia. What is often forgotten is that although the evidence for a genetic contribution to the etiology of these disorders is beyond dispute, no studies indicate that the genetic effects account for all the variation between ill and not ill individuals.

The authors of this paper do not recognize the pseudoscientific nature of biological psychiatry, although, judging from the following statement, they might appreciate the chapter by Kemker and Khadivi in the first edition of the first present book: "Psychiatry derives a remarkable portion of its self-image from pictures of its future. For example, images of a psychiatry based on molecular biology, of the kind rendered by Mullan and Murray and Pardes et al., have had an enormous impact on the types of research that currently receive public funding."

O'Callaghan, E., Larkin, C., Kinsella, A., & Waddington, J. L. (1991). *Familial, obstetric, and other clinical correlates of minor physical anomalies in schizophrenia*. 148, 479-483.

In this study, 41 schizophrenics were divided into two groups based on histories of obstetrical complications while they were in utero. A disorder running in families is taken, pure and simple, as evidence of genetic influence. The thinking, therefore, is flawed in the extreme.

The principal finding was both a greater number of body regions affected by minor physical anomalies and a higher prevalence of mouth abnormalities in the subgroup of patients who had family histories of schizophrenia but whose mothers had not had any obstetric complications. This relationship suggests that familial/genetic factors may determine not only the development of minor physical anomalies but also a particular topography of developmental abnormality. More speculatively, it might suggest that genetic factors relevant to schizophrenia are related in some way to those which determine oral morphogenesis.

The authors are suggesting that the gene for mouth shape and the gene for schizophrenia might be linked. Familial and genetic are treated as synonyms in this intellectual universe.

Maj, J., Starace, F., & Pirozi, R. (1991). *A family study of DSM-III-R schizoaffective disorder, depressive type, compared with schizophrenia and psychotic and nonpsychotic major depression*. 148, 612-616.

This is a well done study with no ideological biases.

Silverman, J. M., Pinkham, L., Horvath, T. B., Coccaro, E. F., Klar, H., Schear, S., Apter, S., Davidson, M., Mohs, R. C., & Siever, L. J. (1991). *Affective and impulsive personality disorder traits in relatives of patients with borderline personality disorder*. 148, 1378-1385.

The authors emphasize genetic factors in a study whose methodology cannot differentiate environmental from genetic influences: "Although environmental influences may play a role in accounting for these familial factors and, as noted, cannot be excluded on the basis of family diagnostic data, the results raise the possibility of a role for genetically heritable personality traits." The phrase *genetic/familial factors* is used by the authors in a fashion that makes the two words seem like synonyms, when actually genetic is a subset of familial from a logical classification point of view, and environmental factors may be intra- or extrafamilial.

Kendler, K. S., Silberg, J. L., Neale, M. C., Kessler, R. C., Heath,

A. C., & Eaves, L. J. (1991). *The family history method: Whose psychiatric history is measured?* 148, 1501-1504.

Very interesting data show that an affected twin reports a higher incidence of her disorder among first-degree relatives than the discordant, nonaffected twin. This is a major confound not addressed in any other family studies during the four years.

Weinberger, D. R., Berman, K. F., Suddath, R., & Torrey, E. F. (1992). *Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins*. 149, 890-897.

I include this paper to emphasize that any studies finding biological differences between twins discordant for psychiatric illness point completely and exclusively to environmental etiology. This is one of the best possible research strategies for proving environmental etiology in psychiatric disorders. Concerning the specific findings, the authors say, ". . . the correlation reported here between a small reduction in size of the anterior hippocampus measured on an MRI scan and a slight diminution in rCBF related to a specific cognitive task may not be found in other groups unless very large numbers of subjects are studied. If this prediction is correct, it raises the question of whether the correlation itself is so rarefied as to be neurobiologically trivial."

Bracha, H. S., Torrey, E. F., Gottesman, I. I., Bigelow, L. B., & Cunniff, C. (1992). *Second-trimester markers of fetal size in schizophrenia: A study of monozygotic twins*. 149, 1355-1361.

The authors studied fingertip dermal ridges in 23 twin pairs discordant for schizophrenia, because fingertip dermal ridge counts are regarded as a marker of toxic effects on the fetus during the second trimester. The findings were that discordant twins had greater intrapair differences than 7 control sets of twins without schizophrenia. However, of the 23 affected twinships, the affected twin had a higher score in 13, and a lower score in 10. The authors state that ridge count is increased in Turner's syndrome (45XO) and decreased in Klinefelter's syndrome (47XXY).

This means that biological insults with opposite effects occur in different syndromes with different known genetic abnormalities, and in a syndrome with a presumed but unproven genetic basis (schizophrenia, which is variably either 46XX or 46XY). The authors conclude: "The study suggests that various second-trimester prenatal disturbances in the epigenesis of one twin pair discordant for schizophrenia may be related to the fact that only one of the twins expresses his or her genetic predisposition toward schizophrenia. This is consistent with a 'two-strike' etiology of schizophrenia: a genetic diathesis plus a second-trimester environmental stressor."

The authors have not explained why one second trimester twin is not affected by the environmental stressor. A more parsimonious explanation for the data is a "one-strike" etiology that is purely environmental, because there is no scientific reason to postulate a genetic diathesis in order to account for the data.

Grove, W. M., Clementz, B. A., Iacono, W. G., & Katsanis, J. (1992). *Smooth pursuit ocular motor dysfunction in schizophrenia: Evidence for a major gene*. 149, 1362-1368.

The authors studied eye tracking abnormalities in first-degree relatives of 92 schizophrenics and 171 controls. This was a total of 146 proband relatives and 171 control relatives. The study assumed the existence of a gene for schizophrenia and proposed that a gene for eye tracking abnormalities could be used to study and locate it. However, the authors stated that "eye tracking accounts for approximately 25% of the variance in risk for a spectrum diagnosis (schizophrenia in addition to schizotypal personality) in schizophrenic patients' families." This is a modest amount of variance, and the prior research should be examined for spectrum-type cognitive errors and for failure to show a finding when schizophrenia alone is considered.

Simpson, S. G., Folstein, S. E., Meyers, D. A., & DePaulo, J. R. (1992). *Assessment of lineality in bipolar I linkage studies*. 149-1660-1665.

Unilineal families are ones in which only one parent has a given disorder; in bilineal families, both parents are affected. The mating patterns of the unilineal family parents are far from genetically random, as noted in another study: "Eighty-five percent of their bipolar inpatients had spouses with histories of some psychiatric disorder, compared to 45% of the unipolar patients." This raises a question as to how unilineal most bipolar families are: many parents rated as unaffected in inadequately designed studies must have "affective spectrum disorders." In a study of children, such cases would be rated as affected in order to support the affective spectrum hypothesis; in a study of parents, they would be rated as unaffected in order to generate a sample of unilineal families. Such methodology destroys the studies.

The only way to avoid this problem is to scrupulously screen potentially unilineal bipolar families for affected coparents. The problem then becomes the massive logistical effort required to locate enough families, given the number of loci to be screened in genetic marker studies. At best, one could detect a minute number of apparently Mendelian pedigrees through such research, but these would be an infinitesimal subsample from a public health point of view, and the number of families required to correct for chance findings would be astronomical.

The authors screened 1,800 bipolar pedigrees and entered 34 families into their study, which involved 96 siblings. Out of five comparisons of rates of different mood disorder categories (bipolar I, bipolar II, unipolar, uncertain, and unaffected) in unilineal and probably bilineal sibs, they found a higher rate of unipolar depression in the bi-lineal sibs (29% versus 6%), which was the only significant finding (chi square= 5.60, df = 1, p < .02). This would not survive the Bonferroni correction.

The authors also assumed that recurrent depressions are genetic and sporadic ones are not, an assumption for which there is no logical or scientific basis. They stated: "The issue of whether even recurrent cases of depression should be considered genetic cases of depression will be reviewed before linkage analysis." Fortunately, they understood, as stated in their conclusions, that "[t]he mode of inheritance of bipolar I disorder is unknown." However, in the succeeding sentences they pro-pose future projects that would cost tens of millions of dollars: "While there may be mendelian dominant forms of the disorder, they may be uncommon. If the current searches for mendelian forms of the disorder are to have the best chance of success, an adequate resource of unilineal families must be studied with DNA markers spanning the entire genome." A methodological question is whether there are enough unilineal bipolar families in North America to support such a project.

Maier, W., Lichterman, D., Minges, J., Heun, R., Ha/mayer, J., & Benkert, O. (1992). *Schizoaf fective disorder and affective disorders with mood-incongruent psychotic features: Keep separate or combine? Evidence from a family study*. 149, 1666-1673.

Rates of affective disorders and psychoses in relatives of 118 patients with schizoaffective disorder or mood disorder with incongruent psychotic features were compared to those in relatives of 109 controls. This involved 475 proband relatives and 432 control relatives. All disorders under consideration (schizophrenia, schizophreniform, schizoaffective, bipolar and unipolar with and without incongruent psychotic features, cyclothymia, and dysthymia) were more common in both sets of proband relatives than in the normal comparison group. The families of the two types of probands did not differ in rates of affective disorder. The data can best be understood in terms of severe mental illness running in families with little or no diagnostic specificity and with no conclusions as to genetic versus environmental causes being possible.

Maziade, M., Roy, M.-A., Fournier, J.-P., Cliche, D., Merette, C., Caron, C., Garneau, Y., Montgrain, N., Shriqui, C., Dion, C., Nicole, L., Potvin, A., Lavallee, J.-C., Piers, A., & Raymond, V. (1992). *Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: Results from the Quebec pedigree studies*. 149, 1674-1686.

The authors reviewed 38 “major linkage studies and workshop re-ports.” They found that in 21 studies it was not reported whether the same diagnostic procedures were used for all subjects, and could con-firm that they were in only 8 studies; blindness of interviewers was not reported in 16 studies and could be confirmed in only 2; independence of diagnosticians reviewing study diagnoses could be confirmed in only 7 studies. The literature contains major methodological flaws that prevent replication or meaningful conclusions being drawn from meta-analyses, and many individual studies.

The authors stated that “unblind diagnosticians tended, for in-stance, to diagnose more affective disorders in bipolar pedigrees than the blind psychiatric board did.” They also commented:

Most of all, our review again indicates that it is imperative that researchers enter only the most severe or definite diagnosis in the first hierarchical level for linkage analysis and that publications provide a minimal description of the diagnostic procedure according to current standards in order to permit replication. Several of the most recent reports do not even provide this information. Finally, our results call for further studies of the impact and origin of this field on diagnosis in pedigree studies.

The authors are setting a low and minimal standard for genetic re-search, which has not been met by psychiatry.

Thaker, G., Adami, H., Moran, M., Lahti, A., & Cassady, S. (1993). *Psychiatric illnesses in families of subjects with schizophrenia-spectrum personality disorders: High morbidity risk for unspecified functional psychoses and schizophrenia*. 150 66-71.

The authors studied 259 first- and second-degree relatives of 30 probands with Cluster A personality disorders (schizoid, schizotypal, and paranoid), and 225 first- and second-degree relatives of 8 controls and 12 subjects with other personality disorders. The pattern of findings was different in first- and second-degree relatives, and there were no significant findings when first-degree relatives only were considered: rates of schizophrenia, unspecified functional psychoses, schizophrenia spectrum personality disorders, depression, bipolar disorder, alcoholism, anxiety disorder and antisocial personality disorder were no more frequent in the first-degree relatives of schizophrenia spectrum probands than in control first-degree relatives. Significance was obtained when second-degree relatives were added, but would have been lost if the Bonferroni correction for multiple comparisons had been done. Adding second-degree relatives to obtain significance violates the genetic principle of higher prevalence in first- than in second-degree relatives. Adding second-degree relatives should *reduce* the degree of difference between groups in a genetic disorder.

This study is close to being a fishing expedition with negative findings.

Bailey, M. J., & Bemishay, D.S. (1993). *Familial aggregation of female sexual orientation*. 150, 272-277.

This study does not suffer from major methodological flaws; however, the authors make an interesting statement about the observed low rate of homosexuality in sisters of index homosexual females:

Because the 12.1% rate implies that the large majority of sisters of female homosexuals are heterosexual, one might be tempted to conclude that familial factors are of minor etiological importance. However, a multifactorial model of transmission, in which one's sexual orientation depends on a conti nuous underlying etiological dimension that is influenced by many genetic or environmental factors each of small effect, can reconcile powerful familial factors with rates such as ours.

The authors are saying that familial factors with weak effects can still be regarded as powerful if analyzed within a “model” that could be used to “explain” everything about human behavior. The model amounts to no more than a statement that human behavior is influenced by many genetic and environmental factors in a complicated fashion. Such statements can be published only in a field with low scientific standards.

Taylor, M. A., Berenbaum, S. A., Jampala, V. C., & Cloninger, C. R. (1993). *Are schizophrenia and affective disorder related? Preliminary data from a family study*. 150, 278-285.

In this study, 1,895 first-degree relatives of 166 probands with schizophrenia, 949 first-degree relatives of 71 probands with affective disorders, and 85 controls were studied for their rates of schizophrenia and affective disorder. The risk of both forms of illness was equal in the two clinical pedigrees, and higher in both clinical pedigrees than in control relatives. The findings indicate that there is no familial, and therefore no genetic, specificity to the two forms of major mental illness.

Silverman, J. M., Siever, L. J., Horvath, T. B., Coccaro, E. F., Klar, H., Davidson, M., Pinkham, L., Apter, S. H., Mohs, R. C., & Davis, K. L. (1993). *Schizophrenia-related and affective personality disorder traits in relatives of probands with schizophrenia and personality disorders*. 150, 435-442.

The rates of schizophrenia-related and affective personality disorder traits were measured in 588 nonpsychotic first-degree relatives of 55 schizophrenics, and 67 probands with personality disorders. Affective personality disorder traits were defined as “one of the hallmark trait of borderline personality disorder, chronic affective instability not attributable to a concurrent major affective disorder.” Schizophrenia-related personality disorder traits were defined as “a condensation of DSM-III criteria for schizotypal and paranoid personality disorders.” In the relatives of pure schizophrenic probands, the rate of pure schizophrenia-related personality disorder traits was 12.3%; in the relatives of pure borderline probands, it was 3.9%. Inversely, in the relatives of pure schizophrenic probands, the rate of affective personality traits was 1.7%, compared to 6.7% in relatives of pure borderline probands.

The authors concluded: “The features associated with schizotypal personality disorder, while familiarly related to schizophrenia, lack specificity for this disorder and may also be found in relatives of probands with prominent affective-related symptoms such as border-line personality disorder.” The finding of lack of specificity echoes the previous study.

An assumption of the study is that borderline personality disorder is in the affective spectrum and schizotypal personality disorder is in the schizophrenia spectrum. However, it is well known that borderline and schizotypal personality disorders overlap extensively in clinical samples, so there is no reason to predict specific findings in family studies. This makes the expenditure of effort required for such family studies questionable, from the point of view of budgeting psychiatric research resources.

Allen, J.M., Lam, R. W., Remick, R. A., & Sadovnick, A. D. (1993). *Depressive symptoms and family history in seasonal and nonseasonal mood disorders*. 150, 443-448.

The authors stated in their abstract: “The genetic loading for mood disorders (of unspecified seasonality), as determined by the family history method, is similar for seasonal and nonseasonal mood disorders.” In the last paragraph of their discussion, they stated: “The demonstration of a genetic contribution to seasonality in mood disorders will require rigorous methods for identifying patterns of mood disorders in family history data collection.” Two pages earlier in the same issue of the *Journal*, Silverman et al. (1993) made this statement: “Family data cannot distinguish between genetic and environmental factors and hence preclude a determination of a genetic relationship between nonaffective symptoms of schizotypal personality disorder and schizophrenia.”

One wonders how such discrepant statements survive the peer review process. Allen et al. (1993) committed the cognitive error that *it if runs in families it must be genetic*.

Mathew, R J., Wilson, W. H., Blazer, D. G., & George, L. K. (1993). *Psychiatric disorders in adult children of alcoholics: Data from the epidemiological catchment area project*. 150, 793-800.

The pattern of data in this study is entirely explicable by environmental factors. In Table 2, the authors present 14 comparisons of the rates of various psychiatric disorders in 408 children of alcoholics and 1,477 matched comparison subjects. The significant findings do not involve an odds ratio above 2.02 for any of these disorders except panic disorder, which has an odds ratio of 4.06 for the children of alcoholics. These are very modest increases in risk. If a Bonferroni correction had been applied, given that the entire Diagnostic Interview Schedule was administered, there would have been only two significant chi-square values: (a) for panic disorder, and (b) for generalized anxiety disorder. However, the prevalence of panic disorder (2.7%) in the children of alcoholics is not much different from general population norms and yields an odds ratio of 4.06 only because the controls have a low prevalence of 0.7%.

Fulton, M., & Winokur, G. (1993). *A comparative study of paranoid and schizoid personality disorders*. 150, 1363-1367.

The authors “found no statistically significant differences in the prevalence of either paranoid traits or schizoid traits among family members of probands with paranoid or schizoid personality disorder.”

Torgersen, S., Onstad, S., Skre, I., Edvardsen, J., & Kringlen, E. (1993). “True” schizotypal personality disorder: A study of co-twins and relatives of schizophrenic probands. 150, 1661-1667.

The authors compared 176 non-schizophrenic co-twins and first-degree relatives of schizophrenic probands to 101 co-twins and first-degree relatives of depressed probands on the frequency of 12 different personality disorders. Table 3 contains 48 comparisons, none of which would survive correction for multiple comparisons. Paranoid and schizoid personality disorders were more common among dizygotic co-twins than mono-zygotic co-twins of schizophrenic probands; the reverse was true for schizotypal personality disorder. This finding contradicts the schizophrenia spectrum hypothesis and the idea that these three personality disorders belong to a single cluster (Cluster A in DSM-IV). In addition, antisocial, borderline, narcissistic, and passive-aggressive personality disorders were more common in dizygotic co-twins of schizophrenic probands than in monozygotic ones.

Among the twins of depressed probands, paranoid personality disorder was more common among dizygotes, and schizoid and schizotypal disorders were more common among monozygotes. The frequency of a given personality disorder was greater among dizygotic co-twins of schizophrenic probands than among monozygotic co-twins for 2/3 Cluster A, 3/4 Cluster B, and 1/5 Cluster C personality disorders. For co-twins of depressed probands, the frequency was greater in dizygotes for 1/3 Cluster A, 0 / 4 Cluster B, and 1 / 5 Cluster C personality disorders. These data are very difficult to fit into any model of true schizotypal personality disorder.

The authors concluded: “The genetic link even between true schizotypal features and schizophrenia is a modest one.” In terms of absolute values, schizotypal personality disorder was found in 3/15 monozygotic co-twins of schizophrenic probands, 1/ 13 monozygotic co-twins of depressed probands, 4/27 dizygotic co-twins of schizophrenic probands, and 0/23 dizygotic co-twins of depressed probands. “Modest” would appear to be the correct term in this context, given the magnitude of the findings and the fact that the problem of equal environments is ignored.

Livesley, W. J., Jang, K. L., Jackson, D. N., & Vernon, P. A. (1993). *Genetic and environmental contributions to dimensions of personality disorder*. 150, 1826-1831.

Subjects in this study were 90 monozygotic and 85 dizygotic twin pairs from the general population who were reared in the same homes. They completed the Dimensional Assessment of Personality Pathology-Basic Questionnaire. The authors claimed to have controlled for the assumption of equal environments, but their attempt to do so was methodologically crude. The most interesting aspect of the authors’ thinking is the following:

The estimates of genetic contributions to some dimensions warrant further comment. Statistically significant genetic differences were not observed for several dimensions, including insecure attachment, intimacy problems, and submissiveness. These dimensions describe interpersonal problems relating to close interpersonal relationships. This is a novel finding that requires replication. One might speculate that these scales refer to problems in the way the attachment behavioral system develops and that, although the system is genetically controlled, differential experiences within the family are primarily responsible for its expression and development. (p. 1829)

The authors were saying that when they find a genetic effect, it is truly present, given that they have demonstrated the validity of the equal environments assumption in their population. However, when they do not find a genetic effect, it is still truly present, but masked by the effect of unequal environments. In reality, the authors have not demonstrated either equal or unequal environments, and the genetic effect they claimed to have demonstrated is a statistical artifact. Their language and tone are those of reductionist biology: they might as well have been talking about ducklings or earthworms.

Inability Of Clinicians To Predict Biological Findings

If the ideological system of bioreductionist psychiatry is sound, clinicians should be able to match clinical diagnosis to hard physical findings, when these are available. Yet they can’t, as demonstrated by the following study.

Risse, S. C., Raskind, M.A., Nochlin, D., Sumi, S. M., Lampe, T. H., Bird, T. D., Cubberley, L., & Peskind, E. R. (1990). *Neuropathological findings in patients with clinical diagnoses of probable Alzheimer’s disease*. 147, 168-172.

In this study, autopsies were done on 25 demented patients who had received diagnoses of Alzheimer's disease on an Alzheimer's Disease Re-search Unit, and 68% actually had Alzheimer's on postmortem. This would seem reasonably good, but the authors failed to correct for chance using Cohen's kappa, a procedure that is part of the basic methodology of any study in which there are two possible categories for subjects' assignment by clinicians (Alzheimer's or non-Alzheimer's, in this study). Using Cohen's kappa, the chance-corrected level of agreement between clinician and autopsy is 0.36, which is far below the level required to be clinically meaningful.

Failure To Consider Severe Childhood Trauma

The failure to consider the biopsychosocial consequences of severe, chronic childhood trauma is a flaw in the methodology of every biological paper reviewed in this chapter. I will discuss only a few papers illustrative of this category of error.

Teicher, M. H., Glod, C., & Cole, J. (1990). *Emergence of intense suicidal preoccupation during fluoxetine treatment*. 147, 207-210.

This was the most influential paper published in *The American Journal of Psychiatry* from 1990 to 1993. It gave rise to a tremendous amount of discussion in psychiatry, in the pharmaceutical industry, on TV talk shows, and in the general media, and it generated many lawsuits and court actions. The paper consisted of six brief case histories of patients who became acutely suicidal while taking fluoxetine (Prozac). Among them were:

Case 3, Ms. C., a 19-year-old college freshman hospitalized "with symptoms of depression, paranoia, bulimia, agoraphobia, and dissociation." While on fluoxetine, she superficially scratched her-self, banged her head, and had to be physically restrained. This profile is not uncommon in individuals with a childhood sexual trauma history and a dissociative disorder.

Case 4, Ms. D., a 39-year-old former executive who "had a history of recurrent major depression, episodic alcohol abuse (in remission), and borderline personality disorder." Her symptoms included "severe suicidal ruminations, dissociative feelings, and the belief that she could not fight or control her suicidal impulses." This is also a trauma-dissociative profile.

Case 5, Ms. E., "a 39-year-old woman with major depression, border-line personality disorder, and temporal lobe epilepsy" who also had "prominent dissociative symptoms." There is no comment on whether she had an abnormal EEG, but a false-positive diagnosis of temporal lobe epilepsy is common in people with undiagnosed dissociative identity disorder.

Case 6, Ms. F., had "multiple personality disorder," according to the authors.

It looks to me like these reactions of Prozac had more to do with the psychobiology of trauma than with anything studied by bioreductionist psychiatry. If this is correct, psychiatry has created a major amount of adverse publicity for itself by failing to consider trauma and dissociation systematically in these six cases.

Signer, S., & Benson, D. F. (1990). *Three cases of anorexia nervosa associated with temporal lobe epilepsy*. 147, 235-238.

This paper is interesting because these authors reported cases of dual personality associated with temporal lobe epilepsy, but the cases did not come close to meeting criteria for a dissociative disorder, and are the best examples of false-positive diagnoses of multiple personality disorder in the entire psychiatric literature (Benson, Miller, & Signer, 1986).

In this study, the authors presented three cases of coexisting temporal lobe epilepsy and anorexia nervosa, and they indulged in lengthy bioreductionist speculations about the etiology of anorexia nervosa.

Case 1, Ms. A., "justified not eating on the basis of examples of Biblical figures, starvation in the world, and God's command." As well, "Her affect was flattened, and hyposexuality, hyperreligiousness, and philosophical concerns were noted." This is far from a typical case of anorexia nervosa, and the woman appears to be chronically psychotic. The authors stated that for 7 months following a right frontotemporal lobectomy she displayed "agitation, overactivity, extroverted behavior, thought disorder, and refusal to eat; she had lost 77 lb. She responded partially to neuroleptics."

This woman has an organic brain syndrome and a psychosis: no conclusions about anorexia nervosa of any kind can be reached from her case.

Case 2, Ms. B., "had occasional ideas of reference and auditory hallucinations (not directed at her), but hyperreligiousness and hypergraphia were not present." The woman's father was an alcoholic, her mother had been treated with antidepressants, and one sister and two brothers had unknown psychiatric disorders. This is again an atypical profile for anorexia nervosa.

Case 3, Ms. C., “reported frequent episodes of depression with suicidal ideation, including six suicide attempts. Her mood was labile, with almost continuous ruminations over how she would feel or react. She was hypergraphic, maintaining copious diaries over many years. Libido was absent. There was no nascent philosophical or religious concern, but she was unable to distinguish important from trivial events. It was uncertain which neurovegetative symptoms had appeared during past episodes, but neither these nor signs of mania were present on examination; many of these episodes had been associated with amnesia.”

For those unfamiliar with the literature, the authors are preoccupied with religiosity, philosophical concerns, and hypergraphia (writing a lot) because these are supposed to be signs of a personality syndrome caused by epilepsy. I suspect that case three had an undiagnosed chronic, complex dissociative disorder and kept journals like many sexual abuse survivors do.

This paper represents biomedical reductionism extended to its extreme.

Rotheram-Borus, M. J. (1993). *Suicidal behavior and risk factors among runaway youths*. 150, 103-107.

The author studied risk factors for running away from home and attempting suicide in 260 male and 316 female adolescents. Childhood physical and sexual abuse were not mentioned or referenced at any point in the paper, except that sexual abuse was noted to be an immediate precipitant of attempting suicide in 4% of cases: this figure was buried in a list of other precipitants in the results section, and not discussed. I expect that the rate of childhood physical and/or sexual abuse in this sample, if measured, would have been higher than the most prevalent risk factor identified, which was depression (54% of children). This was not a biological research study, but I include it to illustrate the extreme nature of contemporary psychiatry's refusal to consider severe childhood trauma, even in populations in which it is likely to be a key factor.

Pseudoscience Concerning The Affective Spectrum Disorders

The idea that many different psychiatric disorders are variants of depression is one of the fixed ideas of bioreductionist psychiatry. Pervasive cognitive errors are to be found in this sector of the literature.

Hudson, J. I., & Pope, H. G. (1990). *Affective spectrum disorder: Does antidepressant response identify a family of disorders with a common pathophysiology?* 147, 552-564.

The authors postulated that bulimia, panic disorder, obsessive-compulsive disorder, and attention deficit disorder with hyperactivity belong to a physiologically caused affective spectrum disorder. They tried to get cataplexy, migraine, and irritable bowel syndrome to fit in the spectrum as well, but classified these as possible forms of affective spectrum disorder, as opposed to the probable ranking given the first four disorders. Their rationale for creation of the spectrum was that these disorders all respond to antidepressant medications, a core cognitive error of bioreductionist psychiatry analyzed in the previous chapter. I also refer the reader to Dr. Pam's discussion of the schizophrenia spectrum in Chapter 1.

The authors mentioned: “It should also be noted that the choice of the word ‘affective’ is arbitrary, reflecting simply the historical fact that antidepressants were generally first used to treat depression and only later found to be effective in other disorders.” If the choice of terminology is scientifically arbitrary, on what was it based? I venture to guess that it was politically strategic in the climate of bioreductionism to call the spectrum affective because this would harness the maximum amount of biomedical prestige, yet clarify that the turf was owned by psychiatrists rather than gastroenterologists (specialists in irritable bowel spectrum disorders) or neurologists (specialists in migraine spectrum disorders).

The findings of subsequently published papers reviewed in this section illustrate the chaotic, contradictory state of findings in biological psychiatry.

Wu, J. C., Hagman, J., Buchsbaum, M. S., Blinder, B., Derriiler, M., Tai, W. Y., Hazlett, E., & Sicotte, N. (1990). *Greater left cerebral hemispheric metabolism in bulimia assessed by positron emission tomography*. 147, 309-312.

This paper could be used as an example of a statement of ideological bias. The authors concluded: “In summary, our findings suggest that women with bulimia nervosa have some specific metabolic brain abnormalities when compared with normal women, anorexic patients, and depressed patients. This suggests that bulimia nervosa represents a distinctive psychiatric illness.”

The study involved doing PET scans on 8 bulimics and 8 controls. There would have been no significant findings with application of the Bonferroni correction for multiple comparisons; there were 13 comparisons in the table, and all significance levels were $p > .03$. The basic finding was that the women with bulimia, when compared to the controls, had lost the normal hemispheric asymmetry in the cerebral cortex.

Martinot, J. L., Hardy, P., Feline, A., Huret, J-D., Mazzyer, B., Attar-Levy, D., Pappata, S., & Syrota, A. (1990). Left prefrontal glucose hypometabolism in the depressed state: A confirmation. 147, 1313-1317.

The authors did PET scans on 10 severely depressed patients before and after treatment with antidepressants, and 10 controls. They observed that the abnormal brain asymmetry found in the depressed state normalizes after successful treatment with antidepressants—the opposite finding from the bulimia study just reviewed. In the depression study, asymmetry is viewed as abnormal; in the bulimia study, lack of asymmetry is abnormal. It is hard to see how opposite findings can occur in related conditions.

Jeike, M.A., Hyman, S., Baer, L., Holland, A., Minichiello, W. E., Buttolph, L., Summergrad, P., Seymour, R., & Ricciardi, J. (1990). A controlled trial of fluvoxamine in obsessive compulsive disorder: Implications for a serotonergic theory. 147, 1209-1215.

In this nicely done paper, the authors found that the less relatively potent and the less relatively selective for serotonin receptors four antidepressants were, the more effective they were for obsessive-compulsive disorder. In decreasing order of clinical efficacy, the medications are: clomipramine, fluoxetine, fluvoxamine, and sertraline. This finding is inconsistent with the affective spectrum hypothesis, but is consistent with the view that there is no biological specificity to any of the disorders on the spectrum.

Goff, D. C., Brotman, A. W., Waites, M., & McCormick, S. (1990). Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. 147, 492-494.

In this paper, the authors found that, in 9 schizophrenics, fluoxetine reduced both positive and negative symptoms of schizophrenia over a 6-week period at $p < .05$. This finding, if replicated, would mean that neuroleptic-resistant schizophrenia would also have to be placed on the affective spectrum, but this would violate the central dogma of bioreductionist psychiatry, which states that affective disorders and schizophrenia are biologically distinct, genetically driven diseases.

McDougle, C. J., Goodman, W. K., Price, L. H., Delgado, P. L., Krystal, J. H., Charney, D.S., & Heninger, G. R. (1990). Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. 147, 652-654.

In this study, the reverse strategy of the previous study was tried. One of three neuroleptics was added to fluoxetine in 17 patients who had what was supposed to be an affective spectrum disorder, and statistically significant improvement in the obsessive-compulsive symptoms was observed.

Kagan, B. L., Sultzer, D. L., Rosenlicht, N., & Gerner, R. H. (1990). Oral S-adenosylmethionine in depression: A randomized, double-blind, placebo-controlled trial. 147, 591-595.

In this small-N study, 9 subjects received active drug and 6 received placebo, with significant differences in antidepressant effect favoring the active drug. The authors stated: “The biological effects of S-adenosylmethionine are myriad, and it is difficult to determine which effects contribute to its therapeutic action.” The study is interesting because it reviews the history of methylation hypotheses of mental illness, and concludes that the current fishing expedition is on the right track (if this is correct, the affective spectrum hypothesis will receive another blow if it is based on serotonergic dysfunction):

Perhaps the most exciting implications of the effectiveness of S-adenosyl-methionine are those regarding the role of methylation in psychiatric illness. The original transmethylation hypothesis of schizophrenia postulated that schizophrenic patients have an overactive methylation system, which puts too many methyl groups on neurotransmitters during their metabolism, thus creating endogenous “psychotoxins.” While the search for these compounds was ultimately fruitless, this hypothesis inspired nearly a dozen studies of methionine loading, which all achieved the same finding: an oral challenge of 10 g of methionine (the immediate precursor of S-adenosylmethionine) causes 40%-50% of patients diagnosed as “chronic schizophrenic” to have acute, transient, reversible psychotic reactions even without overt signs of organic delirium. This highly reproducible finding remains unexplained to this day. Our present results suggest an explanation. It seems possible that many of the patients then diagnosed as “chronic schizophrenic” might today be diagnosed as bipolar or schizoaffective. Thus, the 40%-50% psychosis rate found might represent a consistent rate of misdiagnosed bipolar and/or schizoaffective patients who experienced an acute manic psychosis in response to challenge with methionine. It will be interesting to test this hypothesis with today’s more stringent diagnostic criteria. A more modern version of the transmethylation hypothesis postulates an under-active methylation system in depression and an over-active system in mania.

This is an example of the lurching from enthusiasm to enthusiasm, always with a pretense of progress, that Dr. Pam discussed in Chapter 1.

Wender, P. H., & Reimherr, F. W. (1990). *Bupropion treatment of attention-deficit hyperactivity disorder in adults.* 147, 1018-1020.

This was an open trial of bupropion in treatment of attention deficit in adults, with positive results. The authors stated: "There is a theoretical basis for a therapeutic effect of bupropion in attention-deficit hyperactivity disorder. The drug has dopaminergic activity and attention-deficit hyperactivity is proposed to be the result of a deficiency in dopaminergic function."

There is a "theoretical" basis for an excess or deficit of every transmitter in every disorder, at this level of usage of the term theoretical, which is its standard usage in biological psychiatry. By theoretical, bioreductionist psychiatrists mean a level of intellectual function that falls far below any serious scientific threshold for the theoretical.

According to this author's reasoning, attention deficit disorder should be placed on a spectrum with schizophrenia and should occur when the dopamine hyperactivity of schizophrenia is overcorrected with neuroleptics, which never occurs. Similarly, attention deficit should be treatable with L-Dopa according to this model, but this has never been reported.

McCann, U. D., & Agras, W. S. (1990). *Successful treatment of nonpurging bulimia nervosa with desipramine: A double-blind, placebo-controlled study.* 147, 1509-1513.

In this standard drug study, the authors treated 10 bulimics with desipramine and 13 with placebo, with significant results. However, based on a variety of measures administered, they concluded that the desipramine worked by suppressing appetite, a mechanism that is biologically nonspecific and unrelated to the affective spectrum hypothesis.

McElroy, S. L., Hudson, J. /., Pope, H. G., Keck, P. E., & Aizley,

H. G. (1992). *The DSM-III-R impulse control disorders not elsewhere classified: Clinical characteristics and relationship to other psychiatric disorders.* 149, 318-327.

The authors added intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania to the affective spectrum, using the same logic as in the Hudson and Pope (1990) paper described above.

Wolkowitz, O. M., Reus, V. I., Manfredi, F., Ingbar, J., Brizendine, L., & Weingartner, H. (1993). *Ketoconazole administration in hypercortisolemic depression.* 150, 810-812.

The authors showed that depression can be treated with ketoconazole, a "commonly used imidazole antifungal drug, [which] has prominent cortisol biosynthesis inhibition and glucocorticoid receptor antagonist properties." According to the logic of the affective spectrum hypothesis, we must now consider classifying depression as a fungal infection.

Kahn, R. S., Davidson, M., Siever, L., Gabriel, S., Apter, S., & Davis, K. L. (1993). *Serotonin function and treatment response to clozapine in schizophrenic patients.* 150, 1337-1342.

Although serotonin is supposed to be the biological foundation of the affective spectrum, these authors showed that the serotonin system is implicated in the response of schizophrenia to clozapine.

O'Flynn, K., & Dinan, T. G. (1993). *Baclofen-induced growth hormone release in major depression: Relationship to dexamethasone suppression test result.* 150, 1728-1730.

This study demonstrates an abnormality in GABA in depression, yet another brain chemical that must be accounted for in the affective spectrum hypothesis. The benzodiazepine receptor is close to the GABA receptor on the neuron cell wall, and activation of the benzodiazepine receptor-chloride ion channel-GABA receptor complex is widely presumed to be the basis of the anxiolytic efficacy of benzodiazepines in biological psychiatry. This study raises yet another problem for those who believe in the diagnostic specificity of neurotransmitters.

Altamura, C. A., Mauri, M. C., Ferrara, A., Moro, A. R., D'Andrea, G., & Zamberlan, F. (1993). *Plasma and platelet excitatory amino acids in psychiatric disorders.* 150, 1731-1733.

The authors measured plasma and platelet levels of 8 amino acids in 38 psychiatric patients and 19 controls. The patients included 3 with organic mental disorders, 15 with mood disorders, 13 with schizophrenia, and 7 with anxiety disorders. High levels of plasma glutamate were found in the depressed subjects, coupled with low levels of platelets. This led them to suggest that reduced uptake of amino acids may play a role in depression, yet another complication that must be resolved by any adequate affective spectrum hypothesis.

Conclusion

This completes a detailed analysis of pseudoscience in *The American Journal of Psychiatry* from 1990 to 1993. The January 1994 issue of the *Journal* indicates that logical errors and bioreductionist ideology will continue to dominate psychiatry for some time. A similar analysis could not be made of a leading journal in a truly scientific field.

REFERENCES

- Benson, D. F., Miller, B. L., & Signer, S. F. (1986). Dual personality associated with epilepsy. *Archives of Neurology*, 43, 471-474.
- Carlson, E. B., Putnam, F. W., Ross, C. A., Torem, M., Coons, P., Dill, D. L., Loewenstein, R. J., & Braun, B. G. (1993). Validity of the Dissociative Experiences Scale in screening for multiple personality disorder: A multicenter study. *American Journal of Psychiatry*, 150, 1030-1036.
- Ross, C. A., Anderson, G., Fleisher, W. P., & Norton, G. R. (1991). The frequency of multiple personality disorder among psychiatric inpatients. *American Journal of Psychiatry*, 148, 1717-1720.
- Ross, C. A., Joshi, S., & Currie, R. (1990). Dissociative experiences in the general population. *American Journal of Psychiatry*, 147, 1547-1552.
- Ross, C. A., Miller, S. D., Reagor, P., Bjornson, L., Fraser, G. A., & Anderson, G. (1990). Structured interview data on 102 cases of multiple personality disorder from four centers. *American Journal of Psychiatry*, 147, 596-601.

Research Open

Pseudoscience In

The American Journal Of Psychiatry 2022-2025

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The November, 2022 issue of *The American Journal of Psychiatry* includes a series of genetic studies with accompanying editorials. The methodology of the research has gotten more technical over the last 30 years, with more advanced statistics, but the basic features of the papers have not changed. Psychiatry continues to waste hundreds of millions of dollars annually on research that cannot possibly yield any practical applications. This form of biological psychiatry requires a suspension of common sense and basic logic in order for the funding, grants, publications and academic appointments to continue.

The content and vocabulary in psychiatry have changed over the last 100 years, from psychoanalytic jargon to biological pseudoscience, but the thought processes have not changed. The main new development has been the massive financial influence of Big Pharma: the November, 2022 issue has numbered pages 781-880 but begins with 7 pages of advertising for the drug, Lybalvi, which is a combination of the antipsychotic olanzapine and the opiate blocker samidorphan. The purpose of the samidorphan is to reduce weight gain caused by olanzapine. Olanzapine (Zyprexa) was approved by the FDA in 1996.

Generic olanzapine costs \$50-\$300/month without insurance while brand name Zyprexa costs over \$500. Lybalvi costs \$1,647.18 per month. You can't buy samidorphan by itself but a prescription for the opiate blocker naltrexone is \$25-\$108 per month. You could get separate prescriptions for olanzapine and naltrexone for much less than the cost of Lybalvi.

In this chapter I will review a smaller number of studies than I did in 1995 because it isn't necessary to provide an excessive number of examples of typical papers.

Tabuteau, H. et al. (2022). Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. 179, 490-499.

The strategy of combining a generic drug with a second drug then selling it at a much higher price is common. For example, the generic antidepressant bupropion costs \$6.00-\$11.00 per month. When combined with the cough medicine dextromethorphan and sold as Auvelity it costs \$1,373.00 per month. Dextromethorphan alone costs as little as \$3.57 per month and is found in many over the counter cough medications.

The cost of Auvelity is not mentioned by the authors of a clinical trial about it published in *The American Journal of Psychiatry*: all 5 authors work for the manufacturer, Axome Therapeutics: on the MADRS depression scale, which has a score range of 0-60, the Auvelity group improved by 4.9 points more than the placebo group = an 8.1% greater improvement. Is that difference worth over \$1,300.00 a month?

The November, 2022 issue of *The American Journal of Psychiatry* illustrates the pervasive problems with current genetic research in psychiatry. A primary marketing strategy for bioreductionist psychiatry continues to operate as it did 30 years ago: promises that major breakthroughs with significant clinical results are just around the corner.

Kalin, N.H. (2022). Polygenic risk scores and genetics in psychiatry. 179, 781-784.

Dr. Kalin, in his editorial, writes that:

Key issues the field is dealing with include how to understand the complex interactions among the numerous genetic variants implicated in an illness with critical environmental events, as well as the meaningfulness of the small effect sizes that have been determined from studies linking genetic variation to phenotypes.

The paper that Dr. Kalin is commenting on is:

Lewis, C.M., & Vassos, E. (2022). Polygenic risk scores: On the road from discovery to implementation. 179, 800-806.

In their paper, Lewis and Vassos state that:

As a motivating example, we take the PGSs generated in the largest GWAS for schizophrenia from the Psychiatric Genetics Consortium (PGC), a meta-analysis of 76,755 individuals with schizophrenia and 243,649 control subjects. This study identified 287 independent genetic variants associated with schizophrenia.

PGSs = polygenic scores

GWAS = genome-wide association studies

A GWAS involves taking blood samples and analyzing the DNA in the subjects' blood. A PGS is determined by analyzing the results from a GWAS. A PGS is a statistical measure of the number of "variant" loci or locations in the DNA that are more frequent in individuals with schizophrenia than in controls. These loci are not full genes, rather they are tiny stretches of DNA.

Psychiatrists have no idea how any of the genetic variants identified in GWAS cause any psychiatric disorder or even that they are abnormal – it's all based on statistics, not on understanding the physiology of mental disorders. The overall conclusion from GWAS and PGS endorsed by Lewis and Vassos is that "the liability explained is insufficient for predicting diagnosis in the general population."

So, the results of GWAS and PGS are of no clinical use – nevertheless, according to Lewis and Vassos, as they state in the title of their paper, psychiatry is on the road from discovery to implementation. Such empty promises have been made by biological psychiatry for decades at a cost of many billions of dollars.

Why do GWAS commonly have tens of thousands of patients and tens of thousands of controls? Those numbers project an image of big, high-powered research but actually they are required to get any statistically significant results. The findings are so weak that there would be no findings at all if only one thousand patients and one thousand controls were studied.

In comparison, a study to show that hemoglobin levels are lower in anemic patients requiring blood transfusions than in normal controls would require only 10 people in each group to get statistical significance. That is why I say that there is a failure of common sense in psychiatry – it's obvious that GWAS and PGS studies are a road to nowhere.

Ronald, A., & Pain, O. (2022). A revolution is brewing in how we understand the shared genetic causes of psychiatric disorders. 179, 791-793.

Here again, we have the promise of a revolution. Commenting on Hindley et al (2022), these authors state that:

Genetic correlations can now be estimated from DNA using the results (usually called "summary statistics") from genome-wide association studies, and a statistical method called linkage disequilibrium (LD) score regression is commonly applied. Bivariate LD score regression compares genetic effect sizes for each condition, while accounting for LD, looking across all genetic variants (referred to as an infinitesimal model). . . Hindley et al. apply a method called MiXeR which quantifies the number and proportion of putatively "causal" genetic variants that are unique to and shared across conditions, and then estimates the genetic correlation specifically for the shared loci.

I doubt that there are many psychiatrists in the world who understand such statistical procedures, but you don't need any understanding of statistics in order not to be *bedazzled*. The key phrase in the above quote is "putatively "causal" genetic variants." In biological psychiatry "putatively causal genetic variants" are identified with arcane statistics, with zero understanding of their physiological effects, if any. The futility of the entire enterprise is illustrated in the Hindley et al. paper.

Hindley, G. et al. (2022). Charting the landscape of the genetic overlap between mental disorders and related traits beyond genetic correlation. 179, 833-43.

In Hindley et al. the genetic loci identified in GWAS and PGS are elevated to the status of *causal variants* based solely on statistical correlations with no demonstration of biological causality. The initial sample size in Hindley et al. was 3,571,567 but this was reduced to 268,241 subjects for analysis. The authors identified 5,600 causal variants for ADHD, 8,600 for bipolar disorder and 9,600 for schizophrenia.

However, 8,500 of the variants occurred in both bipolar disorder and schizophrenia, while 1,000 were unique to bipolar disorder and 1,100 were unique to schizophrenia. That finding means that bipolar disorder and schizophrenia are not genetically distinct disorders. If they are genetic brain diseases with minimal input from the environment, then how do the same risk genes produce such distinct clinical pictures? It is obvious that most people with severe schizophrenia are very different from most people with bipolar disorder.

It is scientifically impossible for schizophrenia and bipolar disorder to be distinct genetically-based disorders if they have that degree of genetic overlap; they are very distinct clinically. The only way these research findings on the genetic overlap between different mental disorders can be valid and real is if the *causal variants* are not in fact causing anything clinically: they must be meaningless statistical artifacts.

Also, Hindley et al. take the absurdity of huge sample sizes to a new level - 268,241 subjects. Ten people with cystic fibrosis and 10 normal controls could be distinguished from each other based on clinical findings and genetic analysis with no confusion or overlap.

Another absurdity is the idea that there could 9,600 genetic causal variants for schizophrenia. If schizophrenia was 100% genetic then each causal variant would be contributing $1/9,600 = .0001$ of the total symptoms. There is zero chance that such tiny effects could ever be tracked biologically – plus it would mean that a single person might have to take hundreds or thousands of different medications.

The January, 2023 issue of *The American Journal of Psychiatry* includes a set of papers on autism and ADHD. Schizophrenia and ADHD are both widely agreed to be highly genetic and inherited, but that is based on a statistical slight of hand.

Kendler, K.S. et al., (2022). *An extended Swedish adoption study of anxiety disorder and its cross-generational familial relationship with major depression*. 179, 640-649.

Kendler has done numerous large studies in psychiatric genetics, usually with modest findings, this study being an example. In this study, the authors examined the frequency of anxiety disorders and major depressive disorder in parents and children in a variety of different families: Intact families (N=1,968,352); child not living with father (N=104,243); child not living with mother (N=5,144); stepfather families (N=87,473); stepmother families (N=14,028); adoptive families (N=13,027).

The outcome was tetrachoric correlations between the disorder occurring in the child and in a parent. The most interesting finding was the 50% or greater increase in anxiety and depression when the children were not in an intact family. For example, in intact families the rate of anxiety disorders in children was 13.5% compared to 21.0% in children not living with their biological fathers; for depression the figures were 14.3% compared to 22.7%. This finding clearly demonstrates a major increase in anxiety and depression with a change in family structure.

In a second Table the authors present the tetrachoric correlations for anxiety and major depressive disorders between parent and child in the various combinations of family structure. These range from -0.10 to 0.22 with most of them being between 0.0 and 0.15. These are statistically weak correlations.

The tetrachoric correlations distract from the fact that a disruption in the nuclear family structure (not living with their biological father) increases the rate of anxiety disorders in children by 55% and the rate of depression by 59%. Nevertheless, the amount of research funding devoted to genetics by the National Institutes of Mental Health massively outweighs the funding for psychological and social studies.

Girault, J.B., et al. (2022). *Infant visual brain development and inherited genetic liability in autism*. 179, 573-585.

The authors open their paper by stating that:

Autism spectrum disorder is a highly heritable neurodevelopmental disorder diagnosed in 1 in every 54 children in the United States. Younger siblings of children with ASD have a higher likelihood of developing ASD, where 1 in 5 siblings followed from infancy will receive a diagnosis of ASD by 3 years of age.

That doesn't make sense. If ASD is "highly heritable" why do only 1 in 5 siblings also have ASD? Being Caucasian is highly heritable – 100% of younger siblings from two Caucasian parents are Caucasian.

McMahon, F.J. (2022). *Putting genetics to work in the psychiatric clinic*. 179, 182-188.

The guys have got their lunch pails filled and they are ready to go to work.

Despite the macho vocabulary, what does McMahon say about the state of the art?

The rapid progress in psychiatric genetics over the past 10 years, while exciting from a research perspective, has not yet had an impact on clinical practice. . .

So, is genetics ready to be put to work in the psychiatric clinic? The clinically relevant findings discussed above suggest that we have just begun a journey down a long road of translation.

A long road? We have just begun? We are decades into biological psychiatry research with zero clinical applications, according to biological psychiatrists.

Tadmon, D.T. & Olfson, M. (2022). *Trends in outpatient psychotherapy provision by U.S. psychiatrists: 1996-2016*. 179, 110-121.

It is widely stated that psychiatry is based on a biopsychosocial model of mental disorders, but the results of Tadman and Olfson (2022) do not support that claim. The sample was 29,673 psychiatrists interviewed from 1996 to 2016. The percentage of psychiatric visits involving any psychotherapy declined from 44.4% in 1996 to 21.6% in 2015-2016. In the 2010's, half of all psychiatrists provided no psychotherapy at all.

These changes are not due to any biological discoveries about mental illness, nor are there any new medications that are more effective than those on the market in 1996. Psychiatrists are getting squeezed by insurance companies, hospital corporations and governments into a very restricted role as medication prescribers, a role that is being taken over by non-psychiatrists: primary care physicians, physician's assistants and nurse practitioners.

The image of psychiatrists as treating genetic brain diseases is not working as a strategy to maintain the role of psychiatrists in mental health. Psychiatrists are being squeezed down to the role of 10-minute-session pill pushers. It's only a matter of time till physician assistants and nurse practitioners are able to admit and discharge patients from hospitals and practice without MD supervision – the independent practice component is already in place in some states.

Kittel-Schneider, S. (2023). *ADHD: The mammoth task of disentangling genetic, environmental, and developmental risk factors*. 180, 14-16.

In this paper, the author states that:

The underlying causes of ADHD, however, were unclear for nearly 200 years. Since the beginning of the 21st century, it is largely validated that ADHD is a disorder with a heritability of about 80%, estimated from twin and family studies.

Likewise, it is widely stated throughout the psychiatry literature that schizophrenia has a heritability of 80%.

What is a heritability estimate? It is the result of several stages of statistical manipulation of the raw data. Heritability estimates are a statistical procedure developed for use in plant breeding – the procedure, developed by a man named Douglas Falconer, was imported into psychiatry as a statistical trick to make mental disorders seem more genetic than they actually are.

How are heritability estimates calculated? For schizophrenia, ADHD or any other mental disorder, you take the difference in concordance rates for monozygotic (identical) and dizygotic (non-identical) twins and multiply it by two. Concordance means that if one twin has a disease or trait, how often does the other twin have it? In monozygotic twins, concordance for race, sex, and hair color is 100%, and the same is true for genetic diseases like cystic fibrosis, without exception.

Why is the difference in concordance rates multiplied by 2? The answer is: to make mental disorders seem more genetic than they actually are. For schizophrenia, the best-designed twin studies yield concordances of 22% for monozygotic twins and 7% for dizygotic twins. This means that when one identical twin has schizophrenia, the other twin does not have it over 75% of the time. That fact alone proves that schizophrenia could be at most only a little bit genetic. The actual heritability estimate for schizophrenia is 30% but that is unacceptable to biological psychiatry so something has to be done.

The well-replicated fact that schizophrenia is at most only a little bit genetic threatens the validity of biological psychiatry: biological psychiatry relies on an ideological framework for mental illness of biological brain disease-genetic causation-medication. In the schizophrenia literature, the psychiatry genetics researcher takes the initial heritability estimate and subjects it to two rounds of further statistical manipulation to arrive at a heritability of 80%. The statistical procedures used in such sleights of hand include tetrachoric correlations and structural equation modeling, both of which are incomprehensible to almost all psychiatrists.

Most twin study analyses, both online and in the psychiatric literature, explain Falconer's formula (without mentioning Falconer by name or the fact that the formula was designed for plant breeding) but don't mention the additional rounds of statistical manipulation required to reach a heritability estimate of 80% for schizophrenia.

In a typical ADHD twin study (Langner, Garbe, Banaschewski, & Mikolajczyk, 2013) concordance in male monozygotic twin pairs was 75.2% compared to 15.5% in male dizygotic twin pairs – applying Falconer's formula to these data, the heritability of ADHD would be 120%, which is impossible.

Setting that problem aside, the literature endorses a heritability of 80% for both ADHD and schizophrenia even though the difference in concordance rates for identical twins versus non-identical twins is extremely different in the two disorders. In schizophrenia the difference is 15% compared to 60% in ADHD. That fact proves that the statistical procedures used in the schizophrenia literature to generate a heritability estimate of 80% are not scientifically valid.

Langner, I., Garbe, E., Banaschewski, T., & R.T. & Mikolajczyk, (2013). Twin and sibling studies using health insurance data: the example of attention deficit/hyperactivity disorder (ADHD). *PloS One* 8(4), 1-8.

Parallada et al. (2023) In search of biomarkers to guide interventions in autism spectrum disorder: A systematic review. 180, 23-39.

In this paper, the authors reviewed 280 papers describing 259 studies on humans and 21 studies on animals. Their conclusion was that, "There is currently no response biomarker with sufficient evidence to inform ASD clinical trials." A biomarker is any blood test, scan result, or genetic variant specific for a given disorder. There are no biomarkers for use in either diagnosis or prediction of treatment response for any mental disorder. This fact is stated repeatedly in DSM-5-TR, published in 2022.

The clinical applications of biomarkers in psychiatry is zero after decades of research costing tens of billions of dollars.

Shimelis, H. et al. (2023). Prevalence and penetrance of rare pathogenic variants in neurodevelopmental psychiatric genes in a health care system population. 180, 65072.

These authors studied 90,595 participants with what they called neuropsychiatric developmental disorders (NPDs). These included schizophrenia, autism spectrum disorder, bipolar disorder and intellectual disability/developmental delay. A total of 312 individuals (0.34%) had any of the abnormal genetic variants they looked at. Over 99% of the participants with a so-called neurodevelopmental psychiatric disorder did not have any of the genetic variants they looked for – that finding destroys the genetic-brain disease model of the disorders included in the study.

Shimelis et al. conclude their paper with a sales pitch for further research funding:

Our results demonstrate that at least 1% of individuals in a large health care system population have a rare penetrant single-gene or copy-number variant conferring significant risk for NPDs. This study confirms the important contributory role of rare genomic variants in NPDs and highlights the potential for scientific advancement using genetics-based research approaches. . . in the interim, clinically available diagnostic testing to identify rare pathogenic variants should be offered to symptomatic individuals with NPDs, given the significant personal utility of a genetic diagnosis and the potential to improve outcomes through anticipatory medical monitoring.

There is zero evidence that genetic testing for any psychiatric disorder has any effect on treatment selection or treatment outcome, as stated in DSM-5-TR. This is all hype, false advertising and lobbying for future grant money. A small club within academic psychiatric controls the grant funding, reviews the papers for journals and receives the grant funding.

Besterman, A.D. (2025). Psychiatric genetics in clinical practice: Essential knowledge for mental health professionals. 182, 728-741.

In this 2025 paper, errors of logic and scholarship identified in the original edition of *Pseudoscience in Biological Psychiatry* are repeated 30 years later. Besterman et al. state that:

The field of psychiatric genetics has undergone a remarkable transformation in recent years, driven by rapid advances in genomic technologies, large-scale international research collaborative research efforts. . . These developments have not only expanded our understanding of the biological underpinnings of psychiatric disorders but have also opened up new avenues of research into personalized prevention, diagnosis, and treatment strategies.

That is the same promise made in *The American Journal of Psychiatry* in 1995 - that major clinical applications are right around the corner. No such promises have come true despite being made for half a century or more and none are actually close to implementation. The buzzword currently is *personalized medicine* which means tailoring treatment to an individual person's genetic profile.

How is such prevention supposed to work? You can't change the person's DNA; we don't understand how the *risk variants* are connected to symptoms; there are no medications for preventing symptoms from emerging prior to initial diagnosis; there are hundreds or thousands of risk variants; prescribing psychiatric medications to people before they have symptoms is unethical; such a program

would require screening the entire population to identify people who are at elevated risk for schizophrenia or other disorders; and no insurance company is going to pay for such a “preventive” program.

The dream of personalized medicine in psychiatry would require government-controlled blood testing of citizens with no symptoms, including children. Eliminating childhood physical, sexual and emotional abuse, gang violence, and sex trafficking would do far more to reduce psychiatric disorders than anything *personalized medicine* could ever achieve.

Sha et al. (2025). Copy number variant architecture of child psychopathology and cognitive development in the ABCD study. 182, 763-777.

The authors studied *copy number variants* (CNVs) in 8,564 children with an average age of 9.9 years. CNVs are either abnormal deletions or abnormal duplications of short stretches of DNA.

The conclusion reached by the authors was that, “no CNVRs reached significance” – CNVR = copy number variant region.

Cooper et al. (2025). Prevalence of suicidal ideation and suicide attempts by race and gender in three large U.S. adolescent cohorts, 182, 945-949.

Cooper et al. studied the rates of suicidal ideation and suicide attempts in three different samples of children, one of which was from the ABCD (Adolescent Brain Cognitive Development) Study used by Sha et al. (2025). Cooper said nothing about genes and Sha said nothing about race. Cooper found that “Black girls are experiencing more suicidal ideation and suicide attempts compared to both their White and male peers.”

Melhem, N.M. (2025). What’s behind the increased risk of suicidal behavior in black girls? 182, 901-902.

Possible causes of increased suicidal ideation and suicide attempts in black girls listed by Melhem in her commentary on Cooper et al (2025) are all social and psychological with no mention of genetics. The factors include living in adverse environments, exposure to violence, limited access to mental health services, relationship problems, and racial/ethnic discrimination.

Yalcinbas et al. (2025). Transcriptomic analysis of the human habenula in schizophrenia. 182, 991-1006.

The habenula is a brain region that may or may not be involved in mental disorders. Yalcinbas et al. studied post-mortem brain tissue from the habenula taken from 35 individuals who had been diagnosed with schizophrenia and 33 non-psychiatric controls. The paper is extremely technical and would be incomprehensible to over 99% of psychiatrists.

Following quality control, 16,437 single-nucleus transcriptomes were included in downstream analyses and annotated at broad resolution based on canonical marker gene expression. . . Graph-based clustering identified 17 molecularly defined cell types, including nonneuronal populations (oligodendrocytes, astrocytes, microglia, oligodendrocyte precursor cells, and endothelial cells; N=4,101 nuclei), thalamic neurons (excitatory and inhibitory, N=9,412 nuclei), and Hb neurons (seven lateral and three medial Hb subpopulations, N=2,924 nuclei. . . Principal component analysis revealed that the second and third components of variation differentiated Hb from thalamic neurons and neuronal from nonneuronal cell types,

After many rounds of statistical manipulation, the authors’ final conclusion was:

As with all postmortem human brain studies, we acknowledge our inability to confirm whether gene expression changes are the cause or consequence of disease, or the process of death itself.

Na, P.J. et al. (2025). Environmental, psychiatric and genetic predictors of alcohol use disorder criterion count: analyses of African and European ancestries. 182, 1007-1015.

The authors analyzed data from 11,021 individuals, of whom 5,843 had African and 5,178 had European ancestry. They found that polygenic risk scores predicted 1.3% of the alcohol use disorder criterion count in the African sample and 1.9% in the European sample = the number of diagnostic criteria positive. In contrast. In the African sample, environmental factors accounted for 73.1% of the variance and in the European sample, 58.9% of the variance. Despite this tiny and clinically insignificant contribution by polygenic risk scores, the authors concluded that, “polygenic risk was also a statistically significant predictor.” However, they also stated that, “the predictive utility of PRS is not yet clinically meaningful.”

Ahn, Y. et al. (2025). Relationship between problematic alcohol use and various psychiatric disorders: A genetically informed study. 182, 683-687.

The authors identified a ridiculous number of “causal genetic variants” for problematic alcohol use – statistical correlations are elevated to causal status throughout the biological psychiatry literature, as in this paper - it is commonly stated that genetic factors “underlie” mental disorders, meaning that they provide the fundamental and most important causation. That is an ideologically-driven not a scientific statement.

The MiXeR univariate analysis showed that PAU [Problematic Alcohol Use] was influenced by approximately 6,100 causal genetic variants, which demonstrated pronounced polygenicity.

Gelertner, J. (2024). What are the genetic building blocks of alcohol-related disorders? 181, 952-954.

This paper provides another example of the claim that identifying hundreds of different risk loci represents an advance and brings us closer to clinical applications. The language of “a call to action,” “building blocks,” and “genetic architecture” contributes to the illusion of real science – like psychoanalytic writings from the early twentieth century, the vocabulary sounds technical and authoritative, and contains a high level of ideological certainty, but the substance of real science is absent. The authors claim that:

There has been huge progress in understanding the specifics of the genetics of alcohol-related traits, with hundreds of risk loci mapped at high levels of significance.

Savage, J.E., et al. (2024). Genetic heterogeneity across dimensions of alcohol use behaviors. 181, 1006-1017.

The authors of this paper reviewed health records of 387,105 UK biobank participants. They stated that they could differentiate 18 different drinking behaviors, one of which was a preference for beer. They explained their methodology as:

To empirically model the genetic architecture of AUBs, we conducted genomic structural equation modeling (gSEM) on the genetic correlations between the 18 phenotypes using the GenomicSEM package, version 0.0.5 (23), in R, version 4.2.2 (24). The sampling covariance matrix was smoothed using the nearPD function with a tolerance of 1e-08. We used the psych package (25) to conduct exploratory factor analysis with varimax rotation and the GenomicSEM package to conduct confirmatory factor analysis based on the exploratory factor analysis results. In the confirmatory factor analysis, indicators (AUBs) were retained for each factor with a loading ≥ 0.4 , or the factor with the highest loading if all loadings were < 0.4 . The best model was chosen based on interpretability and fit statistics of one- to five-factor solutions, including the comparative fit index (CFI; ranges from 0 to 1, with values > 0.9 indicating good fit of the model to the data) and the standardized root mean square residual (SRMR; ranges from 0 to 1, with values < 0.08 indicating small residual variance of the data left unexplained by the model).

The authors identified four polygenic risk score predictors of different alcohol behaviors: their analysis resulted in predicting 1.5% of the variance for preferring beer. They concluded that, “the extent to which these factors, or individual phenotypes from them, can be used in personalized medicine, requires further investigation.”

The authors conclude that genetic analysis could lead to a different treatment plan for people who prefer beer over wine or hard liquor, even though polygenic risk score predicts only 1.5% of the variance for preferring beer. They also conclude that further grant funding is required.

Kepinska, A.P. et al. (2024). Familial risk of postpartum psychosis. 181,

The authors reviewed the medical records of 1,648,759 women in Sweden and found that 2,514 (0.15%) developed a post-partum psychosis. However, the siblings of women with a post-partum psychosis had a much elevated rate: 10.69%. Surprisingly, cousins had a rate of 1.78%, which was not statistically different from the rate of 0.15% in the general population.

The authors used the phrase “the risk architecture of postpartum psychosis” and stated that, “the data did not allow us to further disentangle genetic effects from shared environmental influences.”

Actually, the data from this study support the conclusion that genes are at most minor contributors to postpartum psychosis: if there was a strong genetic component to the “risk architecture” then there would have been a significantly increased prevalence among the cousins of affected women.

In the schizophrenia literature, familial risk patterns are used to support the conclusion that schizophrenia is genetic: the relatives of individuals with schizophrenia have an increased risk depending on how closely related they are: monozygotic twins highest, dizygotic next, then half-siblings and parents and then cousins, but cousins still have higher rates than the general population.

So, when cousins have an elevated risk compared to the general population, the conclusion is that the disorder has a genetic component, but when they don't have a higher risk, that should weigh against a genetic component. Instead, Kepinska et al. conclude that they couldn't disentangle the role of genes: they shift the conclusion from negative to neutral.

Zwicker, A. et al. (2023). Polygenic risk scores and onset of major mood or psychotic disorders among offspring of affected parents. 181, 285-293.

The authors studied 1,884 individuals to see if polygenic risk scores predicted who would or would not develop a major depressive or psychotic disorder. They found that, "these PGSs did not improve identification of risk beyond family history."

A polygenic risk score test costs about \$400.00 while family history can be asked about with a few questions and those questions add nothing to the cost of a psychiatric evaluation.

Shimelis, H. (2023). Prevalence and penetrance of rare pathogenic variants in neurodevelopmental psychiatric genes in a health care system population. 180, 65-72.

The authors tabulated the number of "rare pathogenic variants" in 90,455 samples. Out of the entire sample, 312 individuals (0.34%) had a pathogenic variant. They said that they examined 94 genes that they considered to be "high-confidence" for a psychiatric effect. They found that 34.3% of the individuals with a mental disorder had a variant compared to 14.6% of those without a psychiatric disorder. They identified several individuals with a neuropsychiatric developmental disorder who did not have a pathogenic gene variant. The authors recommended that:

In the interim, clinically available diagnostic testing to identify rare pathogenic variants should be offered to symptomatic individuals with NPDs, given the significant personal utility of a genetic diagnosis and the potential to improve outcomes through anticipatory medical monitoring.

There is no evidence that screening for any genetic variant can have any effect on treatment planning or treatment outcomes. Also, as in all such studies, pathogenic variants are identified by statistical relationships in huge samples with no understanding of the biology of how they cause symptoms. The only way to tell that a positive test is a true positive, not a false positive is through a clinical interview, so in principle genetic testing cannot affect treatment planning, which has to be based on clinical diagnosis. The psychiatric literature validates a genetic testing industry that cannot have any clinical utility.

Parallada, M. (2023). In search of biomarkers to guide interventions in autism spectrum disorder: A systematic review. 180, 23-40.

The author reviewed 280 articles that reported on 940 biomarkers for autism spectrum disorder – 755 of these markers were from a single publication. The markers included cytokines, growth factors, measures of oxidative stress, neurotransmitters, hormones, EEGs, eye tracking and MRIs. The author made two comments:

With a median sample size of 64, almost all of the reviewed studies were only powered to identify biomarkers with large effect sizes. Biomarkers assayed in multiple studies yielded mostly inconsistent results, revealing a "replication crisis."

There is currently no response biomarkers with sufficient evidence to inform ASD clinical trials.

These comments by the author highlight several points:

1. Huge samples are required to find any kind of potential psychiatric biomarker whether it be a single blood test or a polygenic risk score. The effects are so weak that they can't be detected with a sample size of 60-100. This fact by itself proves that such biomarkers have no clinical utility.
2. The search for biomarkers has been a shotgun approach to testing hundreds of markers, with no coherent theory or physiological rationale guiding the research.
3. Even when a biomarker is identified in a study it can't be replicated in subsequent studies, including in genome-wide association studies with tens of thousands of patients.

The author, nevertheless, concludes her Abstract with a call for more research:

Systematic "big data" analyses of multiple potential biomarkers could accelerate discovery.

How Effective Are Psychiatric Medications?

Psychiatry promotes its medications as being safe and effective, even though they have many side effects, some of them lasting long after discontinuation of the medication, such as tardive dyskinesia, large weight gains and loss of libido. But what does “effective” mean in psychiatry? It means that the score on the symptom measure drops more on the active medication than it does on placebo. But what does “drops more” mean? It means there is a statistically significant difference between drug and placebo. The problem is that the statistical difference is often clinically meaningless, as in a study by Clayton et al.

The measure of depression used in the Clayton study was the Hamilton Depression Scale (HAM-D). The HAM-D has 17 items and an overall score that can range from 0-52.

Clayton, A.H. et al. (2023). *Zuranolone for the treatment of adults with major depressive disorder: A randomized, placebo-controlled phase 3 trial*. 180, 676-684.

In this study, 266 participants received zuranolone and 268 received placebo. The HAM-D was administered at days 3, 8, 15 and 42. In the Abstract and the Discussion only the results from day 15 are described. Why? Because the results at day 42 did not show any statistically significant difference between drug and placebo. Using a statistic called *least squares mean change*, which helps make the results look better than a simple comparison of arithmetic means, the authors did find a statistically significant difference between zuranolone and placebo.

At day 15 the average HAM-D score change from baseline was -14.1 on zuranolone and -12.3 on placebo. That is a score difference of $1.8/52 = 3.5\%$ on the HAM-D, which is too small to be of any clinical significance.

When large numbers of antidepressant studies are combined, the overall difference between drug and placebo on the HAM-D is less than 2 points, so the zuranolone study is typical for all antidepressants.

Here's the most remarkable part of the story: a two-week supply of zuranolone costs \$16,000.00. That is a bargain compared to the prior version of zuranolone which was only available IV in hospitals at a cost of \$34,000.00 for the medication plus hospital fees for a 60-hour stay. Both forms of zuranolone are FDA-approved for post-partum depression, which was chosen by the manufacturer as a marketing target in order to play on sympathy for new mothers and put pressure on insurance companies to pay for it.

Grant, J.E., et al. (2023). *Double-blind placebo-controlled study of memantine in trichotillomania and skin-picking disorder*. 180, 348-356.

Trichotillomania is a disorder of compulsive hair-pulling which in severe cases can leave large patches of bald head where there was previously hair. A measure of trichotillomania was the Massachusetts General Hospital Hairpulling Scale which has a score range of 0-28. Memantine, a medication usually used for Alzheimer's was statistically superior to placebo for reducing the amount of hair pulling, so would be described as “effective” by the usual standards in psychiatry. The average score reduction on placebo was 3.08 (19.47 to 16.41) while the reduction on memantine was 6.93 (19.30 to 12.37), a difference of 3.85 on a 28-point scale, which is a difference of 13.8%. That is better than nothing but is not a dramatic difference. The most interesting thing about the study is the fact that memantine works on the NMDA receptors in the brain and the glutamate system. Standard antidepressants, often prescribed for trichotillomania work on serotonin and/or norepinephrine systems, so memantine is worth investigating further.

Failure To Consider Severe Childhood Trauma

This is one topic in *The American Journal of Psychiatry* in which there has been some real progress over the last 30 years. Prior to 1995, childhood trauma was never mentioned in biological or medication papers. Examples of papers published in 2022-2025 include:

Zhou, L., et al. (2025). *What do four decades of research tell us about the association between childhood adversity and psychosis: An updated and extended multi-level analysis*. 182, 360-372.

The authors reviewed 183 studies involving 349,265 research subjects. They found that, overall, a history of childhood adversity increased the risk of psychosis by 2.8 times = an odds ratio of 2.8. Unfortunately, the authors never stated what the raw numbers were, which is very important to know. If the base rate of psychosis was 1% in the non-traumatized individuals, it would be 2.8% in the individuals with childhood adversity, but if it was 20% then the rate would be 56% in the traumatized individuals.

Baldwin, J.R., et al. (2023). *Childhood maltreatment and mental health problems: A systematic review and meta-analysis of quasi-experimental studies*. 180, 117-126.

The authors reviewed 34 studies involving 54,656 individuals and found “a small, causal contribution of child maltreatment to mental health problems.” That finding is not believable based on clinical experience and other publications – most likely it was due to including many individuals with low doses of relatively mild trauma. A subset of individuals with severe childhood trauma (ACE scores above 5) would almost for sure demonstrate a strong increase in risk, meaning a double digit increase. But at least the topic is being addressed, which is an improvement on the 1990’s. The historical evolution over the last 30 years goes from we don’t mention childhood trauma, to we mention it but don’t devote any serious research money to it, to we fund some research but the designs are set up to minimize the effects.

Hankerson, S.H. et al. (2022). The intergenerational impact of structural racism and cumulative trauma on depression. 179, 434-440.

A clinical case history in this paper is very illuminating: in addition to intensive structural racism experienced by her family, the African American woman in the case history, who is an adjunct professor at a college in the northeastern United States, experienced multiple adverse childhood experiences (ACEs): her father was incarcerated when she was 17; she was physically and sexually abused by a male relative; and she was bullied by white students at school when they discovered that her father had been incarcerated. She experiences recurrent depression and PTSD and gets triggered by social and political events involving racism. The authors conclude that:

We assert that structural racism and cumulative trauma are fundamental drivers of the intergenerational transmission of depression.

Exaggerating the contribution of genes to mental disorders distracts from and down-plays the role of psychological and social factors. Prior to the ascendance of biological psychiatry in the second half of the twentieth century this function was carried out by psychoanalytical psychiatry, for example through the dogma that adult women’s reports of childhood sexual abuse are Oedipal fantasies.

The entire May, 2022 issue of *The American Journal of Psychiatry* was devoted to structural racism, a topic that didn’t exist 30 years earlier. That’s a very good development but we also need issues devoted to sexual abuse and other forms of trauma.

Conclusion

The overall conclusion from reviewing papers in *The American Journal of Psychiatry*, 2022-2025 is that nothing much has changed in the last 30 years. Genome-wide association studies and risk gene studies have increased in their sample sizes and the complexity of their statistical analyses with no clinically relevant findings. Childhood trauma continues to be under-emphasized. The genetic brain disease model continues to be allocated a disproportionate share of research funding.

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