Acta Psychiatrica Scandinavica 1990: 82 (Supplement 362)

A critique of the scientific status of biological psychiatry

Part I: Errors in Methodology
Part II: Errors in Conception

ABSTRACT--Biological psychiatry has four principal modes of investigation but each has been flawed by errors in procedure and inference such that the bulk of existing findings must be called into question. Pedigree studies are ruined by selective adoption, the use of "throw-away kids" to demonstrate so-called genetic effects, lack of case history data, and lapses in "blind" diagnosis. In particular, the Danish adoption studies are challenged, despite the field's insistence that this research has settled the nature-nurture controversy in schizophrenia. Pharmacological-response studies are the next line of methodology and these are marred by a spurious assumption that drugs which work must be correcting a biochemical imbalance that causes the condition. Thirdly, neuropsychological-neurophysiological studies are "heuristic" fishing-expeditions to find a presumed abnormality to account for psychopathology, without doing the prospective longitudinal research necessary to validate such theory. Lastly, biochemical correlates of emotion are treated as if each emotion must have a distinct neuronal substrate rather than possibly representing a general visceral arousal where cognition defines the feeling. All told, biological psychiatry is often more reductionist than acknowledged, does not come up to current scientific standards, and uncritically cites work which is, or should be, discredited. At the heart of the problem is an implicit ideology within biological psychiatry, with insufficient awareness of its social ramifications: "blaming the victim's body" protects the status quo by holding protoplasm at fault for maladjustment rather than the person, family, or community.

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KEY WORDS: biological psychiatry, biological markers, sociology--medical, eugenics, diathesis-stress model

PART I: ERRORS IN METHODOLOGY

Introduction

As of this moment, impressive progress is being reported in many areas of investigation by biological psychiatry: e.g: 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 many other psychiatric disorders. Indeed, one takes for granted that progress will go on until constitutional mechanisms have been specified for nearly every syndrome so that remedial pharmacological or other interventions can be applied. An indispensable formulary is already available for the treatment of most conditions and the result has been much less reliance on institutional management and qualitatively better lives for mental patients. Biological psychiatry will understandably take much pride in this recent record of accomplishment.

However, all may not be as rosy as might appear at first blush. I do not refer to the lack of exact knowledge as to just what defective genetic or biochemical process is involved in psychiatric disorders because the causes are complex and it will take time to work out the intricate psychophysiological sequences. What I mean is much more fundamental: biological psychiatry cannot properly fulfill its mission because in its current state it has more the accoutrement of a scientific discipline than the substance. This statement will raise skeptical eyebrows, to be sure. It will be the burden of this paper to spell out the grounds for such a broad iconoclastic

assertion. To wit, I will be charged to show: (a) that the methodology and inferences of biological psychiatry are sufficiently flawed as to call into doubt the preponderance of its accepted findings; and (b) that the metaphysical premises—the model of Man—upon which biological psychiatry has been based introduces an extra-scientific bias which shapes the research that is done. In sum, my contention is that an implicit philosophy of "mental illness" has generated the experimental methodology, with the resultant data circularly used to validate the philosophy. My thrust is not to discount biological psychiatry in favor of a purely environmental view of human behavior, but to improve its contribution by dint of establishing more stringent criteria for research design, interpretation of data, and theory-construction.

The plan of this paper is to split the task into two parts. The first section will deal with errors in experimental approach and the drawing of inferences. This section will take as its inception the fourfold classification of methods of research into the "psychobiological interface" proposed by Akiskal & Webb (1): pedigree studies, pharmacological response, neuropsychological-neurophysiological findings, and biochemical correlates of emotion. I will review crucial studies in each of these four areas so as to detail limitations, some inherent in the methods themselves and others arising from faulty application which may have gone largely unscrutinized.

The results of the studies reviewed will be seen as mostly inconclusive at this point in time. This is not to say that there are no genetic or organic factors in psychopathology--only that they remain unproven at the present moment because of serious methodological issues. When the methodology is corrected, the results can be acceptable--but results then may or may not be those that are currently accepted.

The second part of this paper deals with misconceptions, narrow assumptions, and failure to consider alternative hypotheses that biological psychiatrists have inadvertently and unwittingly brought into their work as people (and also as particular people who have chosen this line of work). In an editorial in Biological Psychiatry, Ross (2) chided his colleagues for their espousal of an intrinsic ideology--the *idée fixe* that some biochemical abnormality causes at least a predisposition in nearly every form of psychopathology, culminating in a search for the definitive 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.

My critique of biological psychiatry as an ideology will be chiefly from the perspective of the sociology of knowledge, addressing the social functions of a medical approach to deviant behavior. As an epistemological tool, the sociology of knowledge provides an invaluable means to identify and correct for subjective factors in research praxis. It is the best antidote to a "blind spot" in our scientific field of vision.

We can now pass on to Part I's survey of the four methods delineated by Akiskal & Webb. My emphasis here will be on how their pragmatic application has frequently led to conclusions asserting the existence of requisite, usually prepotent biological factors in the etiology of psychiatric disorders. The review will not attempt to be comprehensive in its treatment of any syndrome mentioned, focusing instead on analysis of technical fallacies endemic across research studies, as well as dubious inductions drawn as a product of overgeneralization, investigator bias, and markedly lower research standards than Lewontin, Rose, & Kamin (3) believe would be tolerated elsewhere in science. The methods in themselves are valid if there are biological variables to measure, but use of the methods (producing a vast literature) hardly constitutes ipso facto proof that the sought-after biological variables exist.

I. Pedigree Studies

The aim of pedigree studies is to determine whether there is a genetic contribution to the development of a given diagnostic condition. 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 virtually 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: consanguinity research, co-twin control cases, and adoption comparisons. Each will be discussed in turn, followed by the latest addition to the methodology--the genetic marker design.

A. Consanguinity Research: Family inheritance is investigated by noting the correspondence of a given diagnosis with degree of kinship and by tracing the psychiatric genealogy of patients (propositi). The latter procedure was followed by

Henry Goddard, a psychologist at Vineland State School in New Jersey, and published in 1912 as The Kallikak Family (4). The propositus, Deborah Kallikak (a pseudonym), was brought for admission at age 8 because her mother's new husband would not accept any illegitimate children; Deborah was diagnosed "mentally deficient" and was taken off her mother's hands for what proved to be a life-long stay at Vineland. Goddard attributed the patient's condition to inherited tendencies going back to the American Revolution when a young soldier had an affair with a "feeble-minded" barmaid, resulting in a line of mental retardates from the child of this brief union ("Old Horror" as he was later called), while after a respectable marriage, another line descended from the soldier resulting in an eminent New Jersey family. Of course 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 (or other retardates) from having any opportunity for a sexual experience, marriage, or discharge from the institution (5). In 1927, the U.S. Supreme Court went further and approved new laws for sterilization since science had now shown that mental deficiency was inherited; the eugenics movement applauded Justice Holmes' brief in Buck vs. Bell ("Three generations of idiots is enough") as a necessary first step toward civilized control of reproduction (4).

Nowadays rarely cited, the Kallikak book has become an avatar of tendentious tracing of psychiatric inheritance. Goddard's tracking of ancestry involved 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 violates the research canon of "blind" diagnosis. Goddard misled critics by stating that he knew the name and biography of the barmaid (Smith's Minds Made Feeble makes clear that he did not) and by retouching the photographs of the "bad" Kallikak branch to make them look sinister (6)! Most remarkably, his genetics are confused, as described by Scheinfeld (7):

> 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!

Yet, no subsequent descendent of the "good" Kallikaks ever displayed "feeble-mindedness", though they numbered in the hundreds by the time Goddard did his survey. Moreover, many of the 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 publication 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 (8)! 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".

Analogous diagnostic partiality can be seen in the hearsay diagnosis of "criminality" in the first modern eugenics study, Richard Dugdale's The Jukes, done in 1887. This genealogical approach to the family inheritance of psychopathology is now considered embarrassing and unworthy of scientific attention because it did not control for the effects of poverty and parental modeling. While Dugdale's data showed high rates of criminality and social parasitism through many generations, the psychopathology can be explained on the basis of environment alone. Thus, the mere fact that some form of psychopathology "runs in families" does not necessarily support a genetic basis for its etiology. What remains pertinent about the Jukes study is that a consanguinity methodology does not, either explicitly or implicitly, point to genetic factors, especially where family, cultural, and economic factors conduce to the psychopathology.

In the area of schizophrenia, Franz Kallmann did hearsay diagnosis of distant or dead relatives, while relying on psychiatrists to classify near relatives of patients they were treating (again not "blind"). He arrived at figures for concordance higher than any other researcher; for instance, 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, Rose, & Kamin (3). Kallmann's work contains at best perfunctory reports on methods and only seldom does he give the case histories that might permit readers to form their own impressions. He does not deal with the genetically-impossible fact

of a schizophrenic who has no family history 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 schizophrenic cases (10). No explanation is offered as to why schizophrenia does not weed itself out of the human population by dint of having no evolutionary value for survival, while reproduction rates are known to be low (11). Like Dugdale and Goddard before him, Kallmann did not adequately consider environmental factors in accounting for why psychopathology is passed from one generation to the next.

In contrast to his continued high status as a pioneer in biological psychiatry, Kallmann's contribution has been called "bloodcurdling pseudoscience" by Lewontin, Rose, & Kamin. 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, he helped draw up the 1933 German sterilization law for mental patients in a committee chaired by Heinrich Himmler. Kallmann imbibed the "taint" hypothesis propounded by Rudin to explain all types of mental disorder, but his own career in Germany was blocked by virtue of being Jewish; he pursued his investigation of schizophrenia as an inherited disease after emigration to the U.S. 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, Rose, & Kamin show that Kallmann never compromised the rigors of science for humanitarian aims: in an early paper he argued for sterilization of schizophrenics and their apparently healthy siblings--just because schizophrenia was "recessive"--so that two Nazi geneticists had to oppose him to protect the large proportion of the German people involved! Perhaps in reaction to the Nazis who went from sterilization of 225,000 mental patients after 1933 to "euthanasia", killing 400,000 mental patients in 1939-40, Kallmann gave up the idea of sterilization and wanted the State to regulate the marriages of schizophrenics and their children, using institutionalization in the last resort to enforce birth control (*à la* Goddard). His attitude towards schizophrenics, and his notion of their "treatment", was frankly proclaimed (12):

> 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.

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 (overlooking any input our society may have had in bringing about that "degeneracy"). Contemporary genetic research into psychiatric disorder has considerably cleaned up its act since Kallmann: e.g. sterilization or institutionalization-*cum*-birth-control are now out of the question, while eugenic ideology can no longer be mentioned in polite society after the uses to which the Nazis put it. In the current scientific climate, Kallmann's crudities are studiously ignored; thus, his work can still be respectfully quoted in nearly every review on the inheritance of schizophrenia! In other words, Kallmann's family concordance rates continue to be treated as bona fide, though outdated scientific data. I take strong exception to this, for I believe Kallmann's work to be discredited. On grounds of lack of a methodology section alone, his results are automatically suspect--his reports should never have been accepted for publication and no reputable researcher should cite his statistics without caveat. Indeed, the problem of statistics without accompanying procedures and records was recently brought home to the scientific community by the Cyril Burt scandal (Burt supplied data on the inheritance of intelligence in bogus twin studies) so that the theory that intelligence is inherited has had to be revised (13). Getting back to Kallmann, his studies are not "blind" and he seemed to have diagnostic suspicions about the relatives of schizophrenics that constituted a marked prejudice much like Goddard's. Moreover, the figures Kallmann presented are routinely inflated: he used an abridged Weinberg method for age-correction, setting the age of risk for schizophrenia at 15-44, so that non-schizophrenic relatives still in that age-frame were only counted half, whereas schizophrenic relatives in that age-frame could be counted whole (14)! When the usual Weinberg formula is applied based on a risk period of 15-40, 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 since the risk period for onset of schizophrenia is essentially between 15-25.

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: outcomes that would be predicted by genetic theory. However, shortcomings in this approach can be seen in Slater's 1968 summary of many studies, including Kallmann's (15):

Expectations of Schizophrenia for Relatives of Schizophrenics

Relationship	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

In the first place, there are inconsistencies. The rates for children of schizophrenics are higher than all other collaterals, but parents' rates (also first-degree relatives) are barely higher than second-degree relatives and are not comparable to that for children or siblings. Second-degree rates, ranging about 2-3%, are slightly above the baseline 1% in the general population; only a large N based on combined samples leads to significant findings.

In the second place, Mendelian rates are not approximated. Given a recessive model of heredity, expectancy rates for first-degree relatives are about 50% and for second-degree relatives about 25%. When both parents are schizophrenics, the expected rate is 100%. None of the figures in Slater's list are anywhere near this magnitude; e.g., a child of two schizophrenics had only a 36% chance of being schizophrenic. Explanations are of two kinds: (a) that environment plays some part in the pathogenesis --but this assumes that genetic factors are already proven; and (b) that "incomplete penetrance" or "polygenetic transmission" complicates the genetic effect, without any basis for this assertion other than conjecture and the plotting of graphs for hypothetical distributions (16).

The most serious breach in inductive logic committed by Kallmann is his use of kinship concordance rates to demonstrate genetic transmission of psychopathology. Since no family inheritance study can control for environment in human research, such evidence is at best inconclusive and at worst misleading (as in the Jukes and Kallikak studies). Because environmental theories also predict that specific disorders will "run in families", genetic researchers can mention family concordance rates to show that hereditary transmission is not excluded as a possible cause, but must move on to other evidence in order to prove that a psychiatric condition is inbred.

B. Co-Twin Control Cases: The next line of evidence in pedigree studies is the comparative rates for a psychiatric disorder in MZ twins vs. same-sex DZ twins, but especially comparing fates of MZ twins reared apart. Kallmann (17) did a very large 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 upon the validity of this figure, beyond the Weinberg inflation. Kallmann defined "identical twins reared apart" by the criterion of at least 5 years separation prior to the onset of schizophrenia in one of them! Since 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 age of 10. In fact, even separation as late as this made a difference in Kallmann's concordance rates: it was 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, Rose, & Kamin: they show that the four most recent studies average out to 26% for MZ twins reared together. Further, 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 *folie à deux*, or some variation of a shared paranoia where each twin plays a central part in the other's delusional system (18). Two recent books on twin symbiosis, by Wallace (19) on elective mutism and Sacks (20) on idiot-savants, speak to ineffable communicative bonds between MZ twins for which there is no analogue between DZ twins. In short, since twins—especially MZ twins—share the same environment, it is not legitimate to construe concordance as fitting a hereditary model. Such interpretation becomes another version of the "runs in the family" argument. Proponents of the genetic point of view do not always appreciate this limitation to the pedigree methodology, as illustrated by Zerbin-Rudin's (21) attempt to rebut any environmental interpretation of twin concordance rates for schizophrenia by the following sophistry:

> 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 round-

about way, we still come back to the importance of heredity.

Kendler (22), in a reprise of Zerbin-Rudin, contended that the environmental similarity of MZ twins is the result and not the cause of their behavioral similarity, thereby making the concordance rates of co-twin control studies amenable to purely genetic attribution. Kendler cited a study to support this contention where physical resemblance of MZ pairs with at least one schizophrenic member did not correlate with concordance. But it is unclear just what this is supposed to prove: the bonds that tie MZ twins are partly based on physical resemblance inducing others to treat them as a unit, but it is also based on intimate contact and common experience--even if they can be told apart on sight. When it is not possible to disentangle joint environment from joint heredity, co-twin control studies have all the problems of consanguinity research.

However, if MZ twins are truly reared apart from birth, then it becomes theoretically possible to do proper genetic investigation. Kallmann's dishonest definition of "reared apart" can be somewhat forgiven because necessity breeds contrived solutions--the research is invaluable and there simply are not enough cases to be found. In one U.S. nationwide survey, a mere 19 cases of MZ twins separated in very early life were identified, and none were schizophrenic (23). When Don Jackson (18) raised questions about the genetic etiology of schizophrenia in 1960, he was able to locate only two cases of MZ twins reared apart in the entire world literature! One of them, reported by Kallmann in a 1938 book based on his work in Germany, concerned 22 year-old Kaete and Lisa, born to a psychotic unmarried mother who could not take care of them. The twins were soon portioned out one to each of the mother's brothers--both 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 highly 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 in 1945 by Craike & Slater (24), actually calls the concordant twin psychoses "folie a 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 as a "brutal" man) and 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 & Slater. Florence was sent to an aunt in London after her mother's death and she remained, also working as a domestic in London, 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 & Slater concluded that Edith was more disturbed than Florence, but that both shared a schizophrenic disease. It can be objected that the history supports no such diagnosis for either twin, and there may have been contamination of independent diagnosis since the sisters were known to be MZ twins.

In 1965, Juel-Nielsen (25) again searched the world literature on MZ-twins-reared-apart and found 2 more concordant cases, as well as 3 discordant, for a box score of 4/7 concordant at that time. The third concordant case came from Kallmann & Roth (26): one twin developed schizophrenia in childhood and the other at age 18; no further details were provided by these authors. The fourth case was reported by Slater (27) and greatly elaborated on by Shields (28) and Gottesman & Shields (29,30); it concerned the illegitimate offspring of a Chinese-English adolescent. Nicholas was in 3 foster homes until age 4, while Herbert was in 2 Roman Catholic nurseries until the same age. Both met for the first time when they were evacuated from London during the Blitz; on their return to the city, their grandmother took custody from ages 6-7. Nicholas was then sent to a stable foster home, while Herbert remained with his grandmother who now 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", but in the end he reluc-

tantly came to a diagnosis of schizophrenia. Upon learning that an MZ-twin-reared-apart existed, Slater arranged for a psychiatric interview of the non-hospitalized brother and was no doubt amazed to hear that the brother 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, with Nicholas learning that their mother had just visited England (she had been residing in the U.S.) and spent time with Herbert. On January 5 Nicholas was admitted to hospital and 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, but early history alone might account for the psychopathology of the brothers and one can only wonder what the impact of their mother's surprise visit was on the child she saw who then sent for the child she had decided not to see.

In 1972, Gottesman & Shields (29) reported more new cases and gave 7/11 as the concordance tally at that time; in 1982, these authors (30) 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 thought; 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 history was offered to assess their environment or how they were diagnosed.

In summary of the co-twin control studies, it is no longer viable to argue that MZ vs. DZ twin comparisons hinge on a genetic differential: environment of MZ twins is much more similar than that of DZ twins, even leading in some instances to symbiotic interaction. Further, investigation of MZ-twins-reared-apart research has yielded too few cases to draw conclusions: of only 12 known cases in 1982, 5 were discordant and of the remaining 7 just the above-described 3 were presented in sufficient depth to be scientifically useful. However, in these 3 cases we have seen that the children were raised 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 some of the cases reported in the literature.

The MZ-twins-reared-apart research is theoretically powerful but in practice the method is limited to naturalistic observation. Because the rare cases "just happen", they cannot be screened to assure good-enough environment conducive to the future mental health of the individual twins. Indeed, the cases are by definition confined to twins whose mothers could or would not take care of them, with the twins separated from each other (but not necessarily at birth) and perhaps ending up in precarious foster situations or institutions. It therefore follows that no reputable scientific paper should uncritically cite these cases as supportive of a genetic theory of schizophrenia, especially when case history data is lacking.

C. Adoption Comparisons: As with the MZ-twins-reared-apart research, adoption comparisons are theoretically capable of settling the nature-nurture controversy; 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 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 influential, most notably that of Heston (31). Heston traced the history of 58 children born to schizophrenic mothers in Oregon state hospitals between 1915-1945. 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 soon after birth, but whose mothers lived in the community and were not known to be schizophrenic. The results for the index and control samples were:

	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
Criminality	9	2
Neurosis	13	7

Heston concluded that his statistically significant results supported a genetic etiology for

schizophrenia. However, statistical significance may be an artifact of a flaw in research design: in Heston's study there is considerable 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, with half spending at least 2 years in institutions because of placement problems (32). In addition, Heston did not take into account that pregnant schizophrenics may not have received adequate prenatal care (11), nor that schizophrenic mothers have high rates of birth complications leading to neurologically-impaired neonates (33). In connection with possible prenatal or perinatal damage, it can be pointed out that the 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 support 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, criminal, or neurotic compared to 9/50 control cases). In short, Heston showed that schizophrenic women were likely to produce children exceptionally vulnerable to early death or emotional disturbance, although it is not demonstrated that this latter outcome is genetically determined since comparatively poor adult adjustment could be explained by a combination of neurological deficit and the difficulties of placing "bad seed" children.

This brings us to the Danish studies, conducted in that country because of its national health register which permits researchers to check the diagnosis of virtually any adult in the population who came to psychiatric attention. Published largely between 1968-1974, the series can be conceptualized as consisting of 3 interlocking investigations:

Kety, Rosenthal, Wender, & Schulsinger (34)--a study of diagnosed schizophrenics who had been adopted in early life, with a comparison of biological vs. adoptive relatives for schizophrenia;

Rosenthal, Wender, Kety, Welner, & Schulsinger (35)--a study of adopted-away children of diagnosed schizophrenics, with a comparison of the incidence of schizophrenia in this cohort vs. other adopted-away children produced by non-schizophrenic parents; and

Wender, Rosenthal, Kety, Schulsinger, & Welner (36)--a "cross-fostering" study which compared rates for schizophrenia when adoptive but not biological parents were 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* study located 33 adoptees who had been 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 amongst all relatives: one in each group and in both less than the 1% expected rate 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 was a statistically significant difference.

The Rosenthal *et al* study located adoptees given up by a parent diagnosed schizophrenic at some point and matched a control group of other adoptees who had no known schizophrenic parent--a design 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 2 Danish groups. In their preliminary 1968 report, 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 results (13/39 index cases vs. 7/47 control cases). In 1971 (37), a more complete report was issued and with an increased N, statistical significance was now claimed (34/76 index cases vs. 12/67 control cases).

The Wender *et al* study compared 69 children of "schizophrenic spectrum" biological parents but raised by non-schizophrenic adoptive parents (the index group) with 28 children of 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 from 5 days to almost 7 years. Based on a new "global psychopathology" interview-based scale, no difference was found between the scores of the cross-fostered and control groups, while the score of the index group was significantly higher than that of the other 2 groups if the latter were combined to make a large enough N.

In many respects the Danish reports are the most impressive pedigree studies yet done and Snyder (38) declared they stand as a landmark contribution. Konner (39) 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". Crowe (40) hailed their collective findings as settling the nature-nurture controversy so far as schizophrenia is concerned. Wender (41) stated on behalf of the research team: "We failed to discover any environmental component". Wender & Klein (42) extrapolated from the Danish adoption data the proposition that 8% of the general population has a personality disorder within the "schizophrenic spectrum" for which there is a genetic predisposition; only medication can correct the underlying biochemical problems. Neale & Oltmanns (14) asserted: "If any doubt remained concerning the importance of genetic factors in schizophrenia, it was abolished by the [Danish] adoption studies". Strong words!

In spite of deserved accolades for a comprehensive investigation, the Danish adoption research is not beyond very serious reproach and does not settle the nature-nurture controversy. It can hardly be contended that the series shows the heritability of schizophrenia; at best they show the heritability of "schizophrenic spectrum disorder"--a vague and possibly non-homogeneous condition. Even scholars as meticulous as Neale & Oltmanns elide this distinction, as can be seen in their above quote. Moreover, biological-psychiatry reviewers often uphold and glorify the Danish studies by virtually disregarding the major criticisms that have found their way into the literature. Already, 4 published critiques exist that simply cannot be ignored, especially in that the last 3 even impugn the scientific integrity of the Danish research team.

Benjamin (43) noticed that none of the biological parents of schizophrenic children in the Kety *et al* study were schizophrenic, while statistical significance came from 9/13 "schizophrenic spectrum" biological relatives who were half-siblings by the father. In short, second-degree relatives had higher rates than first-degree relatives, a result which 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. Kety *et al* said they needed half-siblings to control for potential "intra-uterine sources of schizophrenia", but this claim may have been disingenuous in that without these subjects the null hypothesis would have prevailed.

Lidz, Blatt, & Cook (44) bitterly complained that manic-depressive cases got mixed into the "schizophrenic spectrum" in the Rosenthal *et al* study--and made the difference in achieving significant results because manic-depressive parents were just as fecund as schizophrenic parents in breeding "schizophrenic spectrum" offspring! Since it is held that manic-depressive and schizophrenic genetic processes are distinct, this study too is invalid on its face. In addition, these writers demanded that the Danish researchers publish the data they had from psychological testing of all subjects as an independent means to reach "blind" diagnosis; the pointed implication here was that the Danish researchers were suppressing information presumably unfavorable to their genetic hypothesis.

Cassou, Schiff, & Stewart (45), 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 which are belied by the way cases were reassigned and statistics juggled. Cassou, Schiff, & Stewart also held that adoption studies are automatically invalid if case histories are not presented as to why a child is separated from mother and how the child is subsequently treated. They refer to the probandi as "enfants abandonnés", poignantly suggesting by this terminology that throw-away kids are being used as proof that schizophrenia is genetically transmitted, without any information as to whether the youngsters were neglected, abused, or otherwise damaged before adoption, as well as whether separation from their mother was in itself traumatic. Another issue raised by the French team has to do with when children are placed: few were taken at birth and thus most spent their first 6 months with their natural mothers--the "bonding phase" during which a disturbed woman would have the most harmful impact on her progeny's development (46).

With all due irony, Lewontin, Rose, & Kamin (3) go so far as to insist that the Danish data demonstrates 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 (47) showed that 1-2% of Americans growing up in adoptive homes represent 10% of psychiatric inpatients--Kety's review of the Danish data (48) makes it clear that the adopted-away offspring of schizophrenics fare much better in adulthood compared to their home-raised brethren! Thus, the most important finding of the Danish studies may be an environmental effect: not being raised by a schizophrenic parent may be salutary, provided foster homes are satisfactory. Lewontin, Rose, & Kamin believe the Danish researchers twisted their data to reach congenial conclusions, for example (repeating Goddard's procedure) reporting pseudointerviews with dead or absent relatives based on suppositions as to what they would have said! Further, Lewontin, Rose, & Kamin offer evidence of glossing over the key issue of selective adoption: they show that 24% of index cases had been placed in adoptive homes because a parent had been in a mental hospital vs. 0% for control cases, not to mention that in Denmark children are deliberately placed by foster care agencies in accord with social characteristics of their biological parents (49).

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 (50). At this moment in time, we can only wonder if the glass is half-full or half-empty. Despite the vehemence of such as Paul Meehl (51) 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 1990 that the hereditary basis of schizophrenia is not a proven scientific fact.

D. Genetic Markers: A new methodology in family pedigree studies is represented by the search for anomalies on particular chromosomes which can be traced across generations. With modern technology, a cell-level 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 Egeland *et al*'s paper (52) linking manic-depressive conditions to a single gene on the short arm of chromosome 11; this work was done on subjects from the Amish community in Pennsylvania.

Yet, after making allowance for the 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 demonstrated, with scientific criticism suspended as has largely 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. Confirmation depends on replication of the data across many investigations, as well as by predictions of vulnerability in longitudinal research. Pending such data, scientific judgment of her results must be held in abeyance. Indeed, 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 run in Iceland (53) 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". Both papers brim with high-tech molecular biology, but taken together they stand in contradiction. While Egeland points to family history as proof that depression is inherited, the idea of a "mutation" can supercede family history. The suggestion that different ethnic groups have heterogeneous somatic routes to manic-depression runs counter to the discipline of anthropology and even may deny the unity of the human species. The technology which is supposed to finally identify the predisposing gene for a psychiatric disorder could not consistently implicate chromosome 11, nor was any specific gene mentioned. The "News and Views" editor of Nature, Robertson (54), 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 is right! No one considered in this issue of Nature that perhaps the data shows that medical genetics are not germane to the study of depressive disturbance, and may even be neo-Lamarckian by viewing traits acquired in life circumstances as genetically transmissible.

Following Egeland's lead, linkage studies have now also begun to appear for schizophrenia. Bassett (55) encountered an odd-looking first-admission while on psychiatric duty in a Canadian hospital and learned he 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 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 5q 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 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 way contributed to their schizophrenic condition; 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 more than the circumstantial evidence of a correlation in a single family pedigree.

Bassett's "discovery" led to funding for the next research step: an investigation of 7 families in Iceland and Britain (56), with 2 families showing evidence of chromosome 5 abnormality in their schizophrenic members. However, another study co-reported in the same issue of Nature (57) did not find evidence for chromosome 5 abnormality in schizophrenic Swedish families, but again speculated that mutations could account for differences between ethnic groups. The "News and Views" editor, this time Lander (58), posited that several genes could independently cause schizophrenia, thereby accounting for the incongruent findings. Noting these scientific developments, the Nov. 10, 1988 front page of the New York Times announced the genetic basis of schizophrenia may have been discovered!

By 1989, these early genetic marker studies were quietly retracted (59). The failure to replicate was the main problem; in addition, Egeland found that 2 of her Amish pedigree without the "predisposing" chromosomal abnormality developed manic-depressive disorder.

II. Pharmacological Response

One line of inquiry into the etiology of a psychiatric disorder is pharmacological challenge: determining if any drug can cause the condition, taken to imply that some chemically-similar internal hyperfunction is the biological cause of the condition. Another related line is psychopharmacology: determining if there is a therapeutic effect from administration of a drug, taken to imply that the drug must be supplying an internal deficiency (probably in neurotransmitters) which is the cause of the condition. Both approaches taken together comprise the research methodology of "pharmacological response"; they share the assumption that psychiatric dysfunction has a biochemical basis, with the corollary that drug treatments can be developed to correct homeostatic imbalance and restore mental health. The most obvious problem in this conceptualization is biological reductionism--the attribution of psychological symptoms not to situational factors but to putative bodily states. Further, there is the knotty issue of distinguishing whether bodily states are causing as contradistinct from mediating behavior. The psychopharmacological method has been criticized for *ex juvantibus* logic (60) because it argues from the effect of a drug backwards to the cause of a condition--a fallacy exists since 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, without any known hyperfunction occurring. In fine, while certain drugs can induce behavioral symptoms, and certain medications can alleviate behavioral symptoms, it may be inferentially improper to use pharmacological-response experiments to explain behavioral symptoms in terms of biochemical causes.

A. Pharmacological Challenge: The experimental induction of psychosis in animals or man has a long history (61). In 1845, Moreau de Tour described the mental effects of hashish, and in 1927 Berger reviewed the literature on mescaline, comparing its effect with symptoms of schizophrenia. In 1931 De Jong produced experimental catatonia in different animal species by means of mescaline. Bercel (62) 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 (63), as have amphetamine and cocaine (64). Claims were made that drugs which drive up dopamine levels were repeating the natural action of the brain in schizophrenia. But speculations as to the pharmacological properties of drugs inducing paranoid-like symptoms has so far not led to any breakthrough in schizophrenia research and it remains a question as to how relevant "model psychosis" phenomena are to clinical cases. For example, Hollister (63) shows that clinicians can readily distinguish between drug states and schizophrenic reactions based on mental status examination, while Bleuler (65) concluded that psychotomimetic agents have contributed to our understanding of organic psychosis, not schizophrenia. A toxic theory of schizophrenia must also deal with the fact that "model psychosis" can be experimentally induced by sensory deprivation--an environmental variable. All

that "model psychosis" research amounts to is that toxic substances can cause psychosis, but not that psychosis is caused by toxicity.

The experimental induction of anxiety disorders will be discussed in the later section on biochemical correlates of emotion.

B. Psychopharmacology: With the advent of the phenothiazines in the 1950's, research has focused on why the antipsychotic medications are therapeutically effective. Kety (66) summarized the early thinking by noting the inverse relation between the therapeutic potency of the phenothiazines and its Parkinsonian side-effects: pharmacotherapy for schizophrenia exacerbated Parkinsonism, and pharmacotherapy for Parkinsonism exacerbated schizophrenia. This oversimplified observation 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 can be regarded as an established "finding" in the etiology of schizophrenia by biological psychiatry. It is now known that phenothiazines block CNS receptor sites activated by dopamine--but this doesn't mean that schizophrenia is a biochemical disease since no phenothiazine does more than alleviate some 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.

Despite vigorous laboratory investigation, no psychiatric disorder has thus far been "cured" by medication, not even manic conditions where lithium treatment has been so helpful. In the area of depression research, van Praag & Korf (67) declared the findings concerning anti-depressant medication have failed to revolutionize the treatment of depression, despite the information gained on relationships between metabolism, mood, and motor activity. In the metaphor of Akiskal & McKinney (68) in a paper on theoretical models of depression, 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 backwards in time to precipitating psychosocial stressors.

Research on the efficacy of medications is expected from contemporary psychiatry and biological psychiatry has performed well in the establishment of an ever-improving formulary. But the "fishing expedition" of using response to medication to deduce the 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". Instead, 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 which renders him relatively lethargic, or more precisely, the staff dealing with an agitated patient may be helped by a drug which renders the patient more manageable, with the patient benefitting secondarily (I have seen thorazine used in this manner). In the final analysis, although there is always somatic mediation between stressor and symptom which a drug can alter, the therapeutic effect of a drug can be indirect or even unrelated to the cause of a condition.

III. 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 a rhinoceros. Russell was nonplussed for, according to him, it was not yet certain there was no rhinoceros in the hall; the search must go on. Russell's position was that inductive logic is an endless process which may never finally prove or disprove an inference--common sense must somehow then intervene to set a limit and force a conclusion.

This story may be apocryphal (like the rhinoceros, I can find no substantiation of its existence in the biographies of either Russell or Cohen), 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 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 which at least in part causes it--medicine may not yet know what it is, but is looking for it, and by God will find it! The history of biological psychiatry can be depicted as a tale of "promising" leads, rush to print on slender evidence, hyperbole as initial reception to new work, and ultimately unproductive results. With each failure, the faith remains undaunted, simply

shifting direction in its quest by optimistic lurches from one 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 any "functional" disorder's pathogenesis. From this unfriendly perspective, it will appear that the time must ultimately come to stop a futile search for a presumably 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 pseudoproblem. Moreover, biological psychiatry will insist that considerable progress has been made in tracing out the pathogenesis of disorders such as schizophrenia or panic attacks; the herculean labors will be well worth the effort if we can eventually fix the body as a means to fixing the mind.

All that can 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. In this section, we will look at psychopathy, alcoholism, and schizophrenia as sample topics in the ongoing search for organic factors, not necessarily genetic, which contribute to the onset of psychopathology. We will then critique the findings of biological psychiatry from the angles of sociology and psychodynamic psychology.

A. Psychopathy: Antisocial behavior has been the subject of intense medical investigation for some time. As Hare (69) 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". Thus, the attribution of antisocial behavior to some bodily aberration has fostered laboratory research on criminal populations; the modern history of this research is usually dated back to the work of Cesare Lombroso (70) in Italy 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.

Lombroso branded about 40% of criminals he studied as incorrigible, ascribing their illegal acts to predisposition based on an irresistible "criminaloid" heritage. He distinguished between these "born" criminals (marked by such stigmata as sloping forehead, long arms, prognathous jaw, large incisor teeth, etc.) and "occasional" criminals (normal men driven by desperate or passionate circumstances) in what amounted to a fledgling version of the biopsychosocial paradigm. Lombroso developed rating scales for criminal propensities based on his anthropometric calculations--but he also could explain any case of criminal behavior that did not fit his "atavistic" mold by reference to situational trauma. At the turn of the century, Lombroso's work was hailed throughout the Western world as "the first scientific study of the criminal" since it involved physical measurements and norms!

Ironically, it was precisely the anthropometrics which eventually brought Lombrosian 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" somatic characteristics and criminality. In addition, social criticisms were devastating. The "inborn" inferiority of his criminals ostensibly derived from their constitutional heritage but it was obvious they were being called inferior because they were criminals. Racist aspects were 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 (where they "belonged" and where their rough ways would be useful in exploiting natives for the mother-country). In the 1899 novel Resurrection, Tolstoy (71) has his protagonist 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?"; the Lombrosian answer received in the novel was "arguments as to whether human beings were possessed of free will or not. Could criminal propensities be detected by measuring the skull, and so on? 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 (72) who catalogued physical defects

amongst English prisoners (but dropped "atavistic" implications) and Sheldon (73) who correlated antisocial personality with "mesomorphic" body-build. In a more technological vein, Hare (69) presented evidence showing "maturational retardation" in that psychopaths' EEG readings resembled those of children; Hare also cited findings of autonomic hypoactivity to account for their 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 physiological flaw or even the brain-system involved, nor to any direct causal link. A recent reincarnation of Lombrosian theory concerned the proposition that an XYY chromosomal anomaly produced "supermales" who could not contain their aggression (74). The designation of the cytogenetic XYY as a criminal stigma has since been exposed as a myth (75) and Hare readily agreed--on the grounds that it was not a heritable condition, as his literature review proved psychopathy must be!

Cloninger (76) summarized the case for heritability of psychopathy, referring to the fact that MZ twins have higher concordance rates than same-sex DZ twins (inconclusive evidence, as we have seen), as well as to a pro-genetic Danish adoption study by Mednick, Gabrielli, & Hutchings (77), but he too could hardly venture a guess as to just what biological property is genetically passed, other than to make vague mention of the reticular formation. Cloninger did not critically evaluate research that supported the genetic position, but he did discount a contrary Swedish adoption study because subjects were included whose criminality was secondary to alcoholism. Had Cloninger been more uniformly critical, he might not have missed a much more damaging flaw in the Danish paper whose conclusions he accepted: Mednick, Gabrielli, & Hutchings state that only 25% of their criminal sample were adopted immediately after birth, whereas 51% were adopted within 1 year of placement in an orphanage, 13% within 2 years of placement, and 11% after 2 years--indeed, in a comment unobtrusively located in "References and Notes", the authors reported a statistically significant association was found between later criminality and length of time waiting for adoption! The authors then wondered if this association could be due to the deleterious effect of institutionalization or that the less desirable youngsters were harder to place; in other words, the results of their study could have been produced by a combination of selective adoption and the disruption in bonding inherent in early institutional upbringing.

Sociological criticism of biological approaches to criminality often bears on the issue of "classism" in diagnosis. For example, Cloninger (76) declared that while 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"! As with Lombroso, it appears that there are still two kinds of criminals--shall we say degenerate and respectable types? Sociologists sneer at the presumption that white-collar criminals, as property-owners, will only rarely be psychopathic; their position is that not biological variables but rather class structure and diagnostic bias account for the label's use. The American "muckraker" movement at the turn of the century depicted the leading businessmen of the day--e.g. Rockefeller, Gould, Morgan--as "robber barons" who gathered their fortunes by illicit means but were able to manipulate the political system to thwart prosecution. In short, one man's tycoon can be another man's psychopath. Restated in opposite terms, Cleaver (78) has argued that the street criminal redistributes wealth, sometimes with a rudimentary revolutionary consciousness.

Psychodynamic interpretations of psychopathy focus on early experience as decisive for character-formation. A "superego lacuna" (79) may be the result of identification figures who socialize the child in accord with their own, not the community's moral standards. Social learning theory (80) points to rewards for "bad" behavior, inconsistency in discipline, and especially aggression modeled by parents, peers, and mass media. Stierlin (81) addressed family factors, referring to "delegated" children who are often prematurely thrust out of the home to vicariously act-out their elders' forbidden wishes. Bowlby (82) has written about the "affectionless psychopath" who is unable to empathize and turns against society because of severe maternal deprivation in formative years. In the psychodynamic approach, emphasis is on how the immediate family and community have failed the child, with biological variables viewed as not particularly pertinent to the genesis of the condition.

B. Alcoholism: Alcohol addiction has long been suspected of having some biological component which, in conjunction with opportunity and cultural pressures, causes a "disease". Jellinek defined alcoholism as a progressive disease characterized by psychological and then physiological dependence, while Zwerling derived a typology of alcoholism from the DSM-II psychiatric nosology (83). However, the "disease" model has been attacked because it is not clear whether alcoholism is the disease itself or only a symptom and whether it is a mental or physical disorder (84). Moreover, the voluntary nature of addiction-

causing behavior makes alcoholism non-homologous to any other medical syndrome.

The search for a biological marker for alcoholism includes 8 physical theories offered by the American Medical Association (85): metabolic disturbance, abnormal sugar metabolism, endocrine deficiency, dietary deficiency, liver deficiency, sensitivity to food, dysfunctional "alcohol appestat" in the hypothalamus, and imbalance of the acetylcholine and receptor sites in the ascending reticular formation. After a review of the many different investigations, Madsen (86) concluded alcoholism is a stress disease and he speculated that it originated in the pineal gland! Krimmel (87) noted the many contradictory and inconclusive constitutional theories: missing chromosomes, metabolic deficiencies, lowered blood chloride levels, nutritional deprivation, etc.; he 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'."

Keller acknowledged there are physiological complications in alcoholism but he knew of no research data that they were present before the onset of heavy drinking. Thio (85) added that biological researchers 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".

The most 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 (88). Schuckit (89) has argued that enzymatic mechanisms controlling ethanol metabolism are hereditary and create a biochemical predisposition; his thesis is that higher concentrations mean 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 cautious in the light of measurement problems in biochemical research and the complexities of ethanol absorption but his theory is still purely speculative; the proof of his preliminary 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.

Since the pathogenic constitutional agent has yet to be definitively named, biological psychiatry has in the meantime relied on evidence that alcoholism is a genetically transmitted disease. Two studies are widely cited as conclusive: Goodwin *et al* (90,91) and Schuckit *et al* (92). The former investigation uses the Danish adoption files from the schizophrenic studies to identify a pool of male probandi adopted more or less at birth who had a biological parent hospitalized at some point in life 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 "blind" as to whether they were probandi or controls; the subjects themselves did not know they were participating in an "adoption" study and volunteered no information indicating they knew their birth parents were alcoholic. All subjects were found to be at least moderate to heavy drinkers, with no significant difference between the 2 groups at any level of drinking except for the extreme category "alcoholic" (10/55 probandi, 4/78 controls), leading to the inference that alcoholism is heritable. General psychopathology was rampant, running about two-thirds of both groups according to the 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 3 times more likely to end their marriages) so that Goodwin *et al* 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"! Talk about neo-Lamarckism: it seems even acquired legal status can be inherited these days!

This study has generally been accepted without qualms (93,94). However, in terms of its methodology, 1 or 2 subjects seem to have been mysteriously switched from the control to the index group, while 4 controls were added at the end not "blind" to the Danish psychiatrist. It is impossible to know just what the probandi heard about their birth parents since they were not asked. If the mothers of probandi were the alcoholic parent, there is the possibility of neurological damage in utero and fetal addiction. As always, the question of selective adoption comes up, with "undesirable children" going to less desirable foster homes--a possibility the authors acknowledge.

Schuckit *et al* compared male probandi diagnosed as alcoholic to their half-siblings with whom they may or may not have lived. Since 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 likely suffering from other pathologies, coming from families unusually rent by divorce, remarriage, and redivorce, and probably not representative of alcoholics in general. The study's design does not permit "blind" interviewing since information concerning alcoholic elders must come from the subjects themselves as elicited and judged by the interviewer. Indeed, this very questionable design is credited by the authors to, of all people, Rudin--it is a contemporary experimental application of his "taint" theory! Beyond these devastating issues around research design, the rates for alcoholism are consistently higher for half-siblings raised apart than raised in the same home, which 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 usually lost custody). The data is also unfortunately not analyzed comparing half-siblings by a common alcoholic parent as opposed to half-siblings by a common non-alcoholic parent to see if the exception proves the rule (i.e. what is the effect on children when the custodial parent is the alcoholic?). Finally, as the authors realize, the mate of an alcoholic may have alcohologenic qualities which influence choice of a partner and even the way children are raised.

Sociologists often take umbrage at the findings of biological psychiatry which argue that organic predisposition is necessary in the development of alcoholism. Clear-cut data tie alcoholism to such variables as sex, class, ethnicity, and occupation; this research can be synthesized to form a concept of an alcoholic social role already sufficient to account for differential rates. Trice (95) 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 much greater alcoholism amongst the Irish. Pittman & Gordon (96) called alcoholism an "occupational disease", referring to social functions of alcohol such that every employee on certain jobs became susceptible to eventual addiction through 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.

World rates vary enormously (creating a problem for any predominantly constitutional explanation) and in general immigrant groups to America have much higher rates than in their native lands. Fort (97) has written that we are virtually a nation of addicts, hypocritically pushing a variety of drugs for pleasure or relief.

Psychodynamic approaches are almost as adamantly opposed to the disease model as sociology. Fox (98) pointed out that a physical predisposition was still not demonstrated and then commented:

> 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.

Longitudinal studies of alcoholism, such as that of the McCords (99), typically show a background of broken homes, economic deprivation, and exposure to heavy drinking. Krimmel (87) holds 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 (100) has argued that alcoholism cannot be considered a unitary diagnostic entity; he describes at least 2 subtypes: primary (stemming from an impulse disorder) and secondary (stemming from stress-reduction).

Psychoanalytic theories of alcoholism have centered on 3 themes: oral fixation, repressed homosexuality, and insidious suicide. Research has been notoriously poor in confirming these dynamics, though there are some findings to show alcoholics drink to feel powerful (101), possibly to cover over dependency needs or compensate for narcissistic injuries. Cox concluded 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) psychological factors, especially counterdepen-

dent needs in which alcohol gives the illusion of strength; and (c) sociological factors, such as the "culture of drinking" which influences many people towards progressively heavier consumption. To this day, the most questionable part of this package is the assertion about a "biological propensity".

C. Schizophrenia: Schizophrenia has long been regarded as a brain disease whose arcane nature must eventually succumb to laboratory investigation. Smythies, Coppen, & Kreitman (10) declared:

> For the last fifty years research workers have sought diligently for some biochemical 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.

In chastising the field for "hit or miss" research, Smythies, Coppen, & Kreitman believed in 1968 that biological psychiatry was finally on the right etiological track, basing their optimism on recent research into amphetamine-mescaline psychotomimetic effects. In 1975, Kety (66) too complained that the field seemed very confused when he entered it but now was at last pursuing leads that would provide "light at the end of the tunnel": he was referring to transmethylation studies (attributing schizophrenia to the accumulation of hallucinogenic substances in the brain) and the therapeutic value of the phenothiazines. In terms of neuropsychology, Buchsbaum & Inquar (102) gave the same sort of from-rags-to-riches evaluation of the field's history in 1982:

> A biological test for schizophrenia has so far eluded investigators. Each new neurohormone, each new putative neurotransmitter becomes a candidate--could its 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 widespread support. After a time, even their own developers move on to new transmitters and recordings, abandoning the techniques in the storm of neuroscientific progress.

Buchsbaum & Inquar pointed to the latest work on EEG and PET-scans and had no doubt that significant breakthroughs would now come. It is interesting to note, however, how they characterized an essentially trendy and serendipitous approach to research as a "storm of neuroscientific progress".

Lewontin, Rose, & Kamin (3) pan the assumption of biological psychiatry that schizophrenia must be a biochemical abnormality of the nervous system which 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 (e.g. 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 animal's entrails". They review the last 30 years of this 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.

In a new co-twin control study, Suddath *et al* (103) compared the size of ventricles in discordant MZ twins, with the finding that in 12 out of 15 pairs the schizophrenic member had larger ventricles as well as subtle cytoarchitectural decrements in temporal lobe structures, whereas 7 control MZ pairs did not have this difference. The authors theorized that the schizophrenic twin must have suffered some type of tissue loss 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 morphological changes are simultaneous with or predate the onset of psychotic symptoms. This work has already been hailed as a "landmark" (104), and indeed it is important in view of established clinical findings that organicity is often associated with long-term schizophrenia. However, the meaning of these results is not yet clear in that 12 out of 15 cases is not statistically significant, the study is retrospective not prospective, 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 (as occurred in one of the discordant pairs in the study). Until more data becomes available relating cortical mass to mental health, the research as it now stands is uncomfortably reminiscent of Broca's nineteenth century work which measured "intelligence" by weighing brains (6). Furthermore, in using discordant MZ twins to impute neurophysiological etiology to schizophrenia, biological psychiatry is inherently disavowing genetic factors in schizophrenia, despite an implausible disclaimer by Suddath *et al* that they were merely addressing "extragenetic" effects.

The bottom line here is that biological psychiatry still has no definite idea of the site or mechanism of schizophrenia; van Praag & Korf sadly acknowledged in 1975 (67) that results have been "meager" and urged that research in schizophrenia should henceforth focus on biological correlates of symptoms rather than on the syndrome as a whole. We are left with the puzzle as to whether schizophrenia is basically a brain disease which medicine will ultimately explain, or whether it may be a condition deriving from a psychosocial context. The position of biological psychiatry at this point is to uphold the diathesis-stress approach, in which a biological propensity must be triggered by a noxious environment; as we have seen, biological psychiatry is convinced of a biological propensity because of pedigree studies, as well as the implication of dopamine in the symptom-picture through pharmacological-response research.

Sociological criticism of a biological explanation of schizophrenia often has centered on the strong relationship between social class and incidence; a series of studies have demonstrated that poverty is a significant risk factor, culminating in the work of Hollingshead & Redlich (105) in 1958. Aside from the possibility that diagnosis tends to be more benign when the patient is affluent, the major interpretation of this data is that greater stress faced by the poor contributes to higher rates of mental breakdown. However, Dunham (106) has reinterpreted the data according to a "downward drift" hypothesis which has been endorsed by many biological psychiatrists (107): 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 on faulty parenting as both necessary and sufficient cause. The "schizophrenogenic mother" concept was propounded by Fromm-Reichmann (108) and has more recently evolved into a theory of family communication deficits (109,110) which disorganize and drive the helpless child crazy. Laing (111) went so far as to suggest that the schizophrenic child may be more sane than the family-of-origin! While clinicians are understandably leery of such an extreme position, 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; one can also mention the naturalistic observation of Henry (112) 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). Firmer data has come from Sobel (113) who followed 8 cases where children were born to parents who were both schizophrenic--4 were raised at home and 4 were immediately placed in foster care. Sobel reported none of the foster-raised children were emotionally symptomatic after 18 months of observation, but 3 of the home-reared children were definitely symptomatic by 14 months (unfortunately, Sobel did not follow his cases to an adult diagnosis). In a much more comprehensive longitudinal study, Tienari *et al* (114) reported 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 intensive investigation, Greenspan (115) has shown that children of psychiatrically-impaired mothers were already symptomatic by 3 months of age; reading Greenspan's account of the developmental consequences for the infant of some of the worst possible mothering, one feels sure that these youngsters will be either dead or very soon crazy without clinical intervention. Of the last 3 studies cited, both Tienari *et al* and Greenspan give theoretical weight to predisposing genetic factors in the psychiatric history of offspring of schizophrenics, but they respectively conclude that placement in a proper foster home or psychiatric care for both mother and infant in a joint home can serve as suppressor variables. Nevertheless, in all three studies a noxious family environment can well appear to be cause enough of severe emotional disturbance, even when there

is an academic tip of the hat to biological psychiatry.

In summary, given that it is not possible to ever disprove a constitutional involvement in the etiology of psychopathy, alcoholism, or schizophrenia, a wide array of theories have been proposed and reviewed. We have noted the same serendipitous and trendy search in all three areas to identify some organic factor which presumably causes the condition, with a succession of studies into "promising leads" that seem to always represent themselves as the long-awaited breakthrough in a steady stream of scientific progress. Thus far, when it comes to organic etiology in biological psychiatry, *le plus ça change, le plus c'est la même chose.* We have also noted many scholarly assurances that the elusive constitutional mechanism must exist and is just waiting to be discovered, basing such claims on genetic studies which are somehow not subjected to critical examination, though there may be criticism of contrary findings. Finally, we have noted the inability or unwillingness to consider the contingency that sociological or psychodynamic variables are adequate to account for the psychiatric condition; instead, biological psychiatry tends to insist on an ostensible biopsychosocial paradigm which is too often mainly biological determinism.

The above comments do not imply that any of the syndromes at issue are purely psychosocial in nature--any might eventually be shown to have somatic dimensions to its etiology. The present paper cannot dismiss this possibility, however substandard, inconclusive, or contradictory some of the past research may have been.

IV. Biochemical Correlates of Emotion

The search for biological markers in anxiety or depressive conditions is especially hopeful in that affective phenomena by definition must be somatically expressed. Nevertheless, research is complicated because not only psychophysiological processes need to be studied but also metaphysical (mind-body) questions have to be resolved which have long stymied human inquiry.

The very first issue is semantic: what is "emotion"? Rapoport declared that we cannot clearly say since we regard emotion as both a phenomenon and a dynamic (116). 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 and also which and how many these are (117). Moreover, while there are undoubtedly physiological correlates of emotion, it is not certain that this implies physiological specificity (i.e. a characteristic neurochemical substrate for each emotion which is the same across people). Controversy has swirled around the causal sequence in emotion: does the psychological aspect precede and trigger the somatic aspect, or vice-versa? The James-Lange theory holds that the body reacts to a perception and the 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, with "downwards discharge" activating the viscera (ANS) and the muscles (CNS), while "upwards discharge" subsequently informs the cortex and gives the "feeling tone" of an emotion (118). James-Lange theory is a process explanation of emotional consciousness (119) 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 (120) 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 Cannon-Bard theory, suggesting 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, in the Cannon-Bard view, 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 cognitively initiated and structured to determine a specific emotion.

The next issue concerns the fact that "emotion" is an evolutionary constituent of the human being; since this is so, we are presented with a phylogenetic conundrum when it comes to "emotional disorder". Is such pathology normal behavior in the face of perceived stress (though thresholds may be quite low), or is it abnormal neurophysiological functioning that makes situations stressful? The investigations of biological psychiatrists 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 correct, all that can be demonstrated by such research is that autonomic reactivity correlates with symptoms, but there will be no premorbid marker common to propositi. Even if biochemical abnormalities are found, we still don't know that these "cause" emotional disorders, since constitution is a basis for affective experience, but not a determinant; biology sets a limit on what behavior can be, but is not able to dictate its content (121). 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 issue arises from nosological classification of anxiety and depressive conditions into discrete types. Does each subcategory have its own distinctive biological workings and thus responds to different medications, or do the various subtypes share a common physiological mechanism? Are anxiety and depressive conditions themselves differentiable on a neurochemical basis? Current answers are far from conclusive, ranging from insisting that research address each subcategory separately because underlying pathophysiology is different (122) all the way to arguing that genetics are the same for anxiety and depression and only environment makes them different (123).

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

A. Anxiety Disorders: Panic attacks are nowadays widely held to be accessible to biochemical explanation; Sheehan (124) commented in 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.

The hereditary aspect of panic disorder is reviewed by Crowe (125) who summarized research to set a life-time prevalence rate of 2-5%, whereas consanguinity studies showed a morbidity risk in first-degree relatives of up to 61%. 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 (126) 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 assumed environment was equally similar for both kinds of twins--a premise that is just 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 for biochemical abnormality, attention has focused on the chemical induction of panic disorder through lactate infusion, carbon dioxide inhalation, or the administration of yohimbine, caffeine, or isoproterenol (127). The most intriguing results were reported by Pitts & McClure (128) in 1967; they provoked panic attacks in the laboratory 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 attained only with maximum muscular exertion or after administration of adrenalin. Nevertheless, attempts to make lactate level the biological marker for panic disorder have failed (129); metabolism of sodium lactate to bicarbonate is so swift that blood lactate levels do not elevate following infusion (130), 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 (131) 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. 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, if lactate is a factor in the biochemistry of panic disorder, it is only a mediator; specific environmental events (the phobic object or situation) incite a fight-or-flight somatic reaction, while lactate infusion is most apt to produce panic in those who have been traumatized before. Thus, sketching in the biochemical processes, two phases would be necessary: first, 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); and second, the visceral reaction of "suffocation" feeds back into the perception of threat (a James-Lange sequence). This account still leaves unsettled the problem as to why some people are more

susceptible than others to the perception of threat from non-malignant sources, and the theoretical gap can perhaps best be bridged by referring to associations from one's past as instrumental in starting the psychosomatics. The cognitive-visceral interaction is obviously a good deal more complicated than is indicated by Carr & Sheehan's (132) conclusion that "panic disorder is a biological disease... [It is] but one consequence of a primary brain-stem neuronal dysregulation".

Considerable research has also been done relative to other aspects of the biochemistry of anxiety; in summary, this work amounts to rounding up the usual neurotransmitter suspects: e.g. catecholamines, adrenergic receptors, and GABA have been studied, but without substantial results (133). Although sympathetic overstimulation has long been assumed in panic disorder, many findings indicate parasympathetic abnormalities as well, so no simple theory can accommodate all the data (131). 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, some books have appeared in the popular psychology literature which attribute anxiety conditions to inner ear dysfunction (134) or poor nutritional balance (135).

Another area for research has been obsessive-compulsive disorder. Hollander *et al* (136) 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 researchers then hypothesized that such patients have overly sensitive serotonin receptors. The researchers also found that intravenous injection of the antihypertensive drug clonidine led to reduction in symptoms, suggesting to them that the neurotransmitter norepinephrine moderates anxiety triggered by the disorder. Some difficulties with these inferences are that in model-neurosis designs, drugs may affect many sites of action; the question is begged as to just what triggers serotonin, etc. as a "biochemical determinant of anxiety"; and it is not demonstrated that afflicted individuals have a premorbidly higher sensitivity to whatever triggers serotonin. It is especially troubling that subjects who respond to biological challenge already have an obsessive-compulsive disorder: this could mean that subjects who respond to stress with obsessive-compulsive symptoms do so in laboratory experiments too, but not that the laboratory procedure addresses their specific "biochemical" predisposition. Also, it must be remembered that laboratory responses are <u>not</u> necessarily tantamount to real-life responses, given insidious "demand characteristics" imposed when one becomes a subject in someone else's experiment (137).

B. <u>Depression</u>: 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 feeding back alerting and confirming messages about one's emotional state to the cortex. In this model, psychopathology derives from an external situation perceived as destructive (or from a personality disorder such that the external situation is interpreted as if it were dire); somatic aberration is not necessarily part of the model, except as a result of chronic reaction which may do physiological damage in due course. This theoretical approach is not one that biological psychiatry tends to endorse; their investigations are usually based on a search for biological markers which are presumed to be etiologically crucial, represent some sort of biological abnormality, and may be inborn. Thus, our review can start with the contention that depression has a genetic foundation: patients with an affective diagnosis are often seen as having inherited a latent "predisposition" just waiting to be triggered by the incidental miseries of life.

Gershon (138) regards the genetic transmission of depression as a settled issue, so that in his account of the evidence for heritability he prematurely intermixes the next issue: what is the pathophysiological vulnerability and involving what gene or genes? His manifest bias aside, data in support of his genetic thesis starts with consanguinity studies, though Gershon acknowledges these are highly inconsistent in reported rates, partly because of differences in procedures and criteria and partly because of cross-cultural differences in prevalence. While aware there can be no "true" rate of diagnosable affective illness, Gershon still argues heritability because within-study comparisons show that relatives have higher rates than controls--the old "runs in the family" fallacy. He then cites MZ-DZ twin research to show higher concordance rates in the former group--the other potentially misleading methodology which cannot neutralize environmental differences as an extraneous variable. Gershon does refer to an MZ-twins-reared-apart study (comprising no less than 12 pairs from one country!) but he is leery of its findings because of the lack of systematic sampling. Gershon realized that adoption studies are critical to any demonstration of genetic etiology but unfor-

tunately he could point to only one such investigation, dealing with bipolar disorder. This is the report of Mendlewicz & Rainer (139) which, parallel to the Danish adoption studies in schizophrenia, was only able to get significant results by creating an "affective spectrum", including bipolar, unipolar, cyclothymic, and schizoaffective diagnoses. Working in Belgium, Mendlewicz & Rainer found 31% of the biological parents of adopted bipolar probandi to have "affective spectrum" disorder, nicely comparable to the 26% rate found in parents of bipolar patients raised at home, but significantly higher than the 12% rate found in the adoptive parents. The genetic interpretation of the data by the authors is weakened by the failure to give any case history information, so that we never know why or when the children were given up for adoption, or if there were long stays in temporary shelters or institutions before placement. We also do not know if the children ever knew their mothers were psychiatrically ill (no fathers in their sample were in the "affective spectrum"), nor if there was contact with the natural mother after placement. Moreover, generally speaking, the mental health of adoptive parents is likely to be better than that of biological parents (especially those who give their children up for adoption) because adoptive parents are screened for mental health before they receive custody from a foster care agency.

Gershon winds up his survey of evidence for the genetic point of view by referring to preliminary data on an adoption study of suicide; using the Danish adoption 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 *et al* (140) 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 form of psychiatric treatment at the time of their suicide. Clayton (141) questioned such logic on the grounds that not being in treatment does not preclude having a psychiatric disorder! Kety's interpretation of the same Danish family data (142) is even more problematic: he regards suicide as a brain disease *tout court*. Kety thinks of suicide as analogous to pellagra which was initially found to follow kinship lines until Goldberger in 1915 showed the mechanism of transmission to be a deficiency in B vitamin niacin--the family ate the same food! Kety expects somatic deficiencies to be discovered for all mental disorders which, for now, only can be said to run in families, with exact mode of transmission unknown. But Kety's use of pellagra as an analogy for suicide is curious: pellagra has an environmental cause, whereas Kety insists suicide is a hereditary condition, with much of the evidence for this being family concordance rates. In addition, neither of the above studies deals 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 which must underlie depression (and suicide) if the condition is inherited, research has followed the fixed conviction of biological psychiatry--namely, that abnormalities in neurotransmitters are the source of psychopathology. While no definite findings have yet been established, extensive research has been done based on pharmacological response because manic-depressive states can be altered by drug therapy. Schildkraut *et al* (143) are impressed with the pathophysiological complexities of depression but feel confident that the emerging field of psychiatric chemistry will discover new medications that will give clues to the various mechanisms resulting in different forms of depression. These writers 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", while still other researchers have stressed the role of acetylcholine. To complicate matters further, Schildkraut *et al* pointed out that depression is a neuro-endocrinological-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 which causes the psychopathology. This is an unabashed medical-model approach to depression, with cognitive and situational variables reduced to an epiphenomenon of merely academic interest.

Conclusion to Part I

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 research procedures or interpretation of data must not be accepted for