Schizophrenia and Platelet Monoamine Oxidase: Research Strategies

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Abstract

The most widely replicated neurochemical finding in schizophrenia is that of lower levels of monoamine oxidase (MAO) in the platelets of chronic schizophrenics than in normal controls. Yet, the etiological role of MAO in schizophrenia remains to be demonstrated. The incidence of low MAO in other psychiatric disorders, effects of diet, hormones and drugs, and relationships of platelet MAO to brain levels and genetic mechanisms remain unclear. This article examines factors which make any biological indicator suitable for use as a diagnostic test for schizophrenia and inquires into the methodological pitfalls and unexamined assumptions of various research strategies which use this measure.

The finding of lower levels of monoamine oxidase (MAO) in platelets of chronic schizophrenics than in platelets of normal controls, first reported by Murphy and Wyatt in 1972, has now received more widespread replication than any other neurochemical finding in schizophrenia. Combining probabilities across 14 (Buchsbaum and Rieder 1979) or 31 (Wyatt, Potkin, and Murphy 1979) published studies drawing patients from multidisciplinary research hospitals on three continents yields far less than 1 in 10⁶ that such distributions arise by chance. In this special issue of the Schizophrenia Bulletin devoted to MAO, Wyatt and co-authors (p. 199) present an overview of the extent of this research. Has the elusive etiology of schizophrenia now been demonstrated? Are the results the product of some pervasive but occult artifact? Is the crucial yes or no investigation still needed?

The purpose of this review of the Proceedings of the National Institute of Mental Health (NIMH) Conference on Schizophrenia and Platelet MAO is (1) to examine the factors which make any biological factor suitable for use as a diagnostic test in schizophrenia, (2) review the ways a biologic marker can relate to a clinical syndrome, and (3) inquire into possible methodological pitfalls and unexamined assumptions of the various research strategies which use this measure.

Requirements of the MAO Factor for Schizophrenia Research

There are at least five major presuppositions that require empirical support before one can accept with some assurance the utility of MAO blood platelet activity assays in the diagnosis of schizophrenia, and the underlying neurochemical-psychological mechanisms upon which this research is based.

The first prerequisite is that platelet MAO activities can be reliably measured. The second assumption that requires evaluation is whether platelet MAO activities are generally stable characteristics of individuals, and to what extent they can be influenced by transient environmental factors such as diet, hormones, or drug use. Thirdly, a related, more specific question is the extent to which platelet MAO activities are under genetic control. Fourthly, there is the large question of whether platelet MAO activities can be meaningfully related to brain MAO activity and to neuronal func-
tion. And finally, the fifth question is whether there exist stable, replicable correlates of MAO activity with psychological traits and behavior.

**Measurement Reliability.** Human platelets contain readily assayable amounts of MAO activity when radioactively labeled amines are used as substrates for the enzyme. A 20-fold range of MAO activities was observed in the largest group of normal subjects (680 individuals) reported in the literature (Murphy et al. 1976). Variations do occur within subjects, but they are small compared to between-subjects differences.

Assay replicability and reasonable test-retest reliabilities are critical; a result which identifies a patient as low MAO or not each time a blood sample is drawn is necessary for clinical applications where individual patients are assessed (as compared with a more basic study where group mean differences might suffice).

Assay sensitivity may be considerably less when certain substrates (e.g., serotonin) are used (Donnelly and Murphy 1977) and also may be lower when spectrophotometric or fluorometric assay methods rather than radioenzymatic procedures are used. Although high correlations have been found between results obtained with different substrates (as Zeller and Davis point out on p. 267 of this issue), some investigators have reported apparent differences in platelet activities (particularly in individuals with psychopathology) when platelet MAO activities with different substrates are compared (Demisch et al. 1977; Melzer and Stahl 1974). Careful attention should be paid to substrate concentrations in relation to the Michaelis constants (Kₘ's) of the enzyme, as discussed by Wise and co-workers (p. 245).

Differences in the collection, preparation, and enumeration of platelets are also important factors potentially limiting assay reproducibility, and they undoubtedly contribute to the variability in results reported from different laboratories. Platelet centrifugation procedures, in particular, may yield platelet populations of different density and size, with corresponding differences in platelet MAO activity (Murphy et al. 1978a). In this issue, Corash (p. 254), Jackman and Meltzer (p. 259), and Wise and co-authors (p. 245) describe alternate techniques for obtaining the platelet. Friedhoff and Miller (p. 314) raise the issue of the effect of physiological factors on platelet characteristics and potential artifacts that may occur in MAO measurement. Further, the intriguing possibility that an endogenous MAO inhibitor might be present is explored by Vogel, Ladman, and Berrettini (p. 232). Future research needs to explore whether chronic schizophrenics with low MAO have platelet sizes that differ from schizophrenics with normal levels of MAO. Such an approach presumes that all schizophrenia is not related to low MAO activity and avoids the assumption that schizophrenia is biologically homogeneous.

**Platelet MAO Activity: Stability Over Time and Changes in Relation to Hormones, Age, Diet, Drug Action, and Psychiatric Status.** In order to carry out research on the relationship of biochemistry to behavioral expression, there must be some stability in the biological factor or at least some known lawfulness about its variability. The intradividual MAO activity level is generally stable over long periods of time and under a variety of conditions. Yet there are factors which seem to affect it, including hormones and the menstrual cycle, age, diet, drugs, and changes in psychiatric status. Robinson and Nies (p. 298) and Sullivan and co-workers (p. 308) review these factors and note the importance of controlling for age and sex in MAO studies.

Little work has been reported on the effects of diet on MAO activity, and presumably MAO is not significantly altered by food ingestion (Belmaker et al. 1974; Post and Murphy, in press), although the effects of short- and long-term nutritional differences have yet to be evaluated. An exception, Sourkes (p. 289) discusses the finding that iron deficiency anemia is associated with reduced blood platelet MAO activity and the possibility that riboflavin deficiency may also affect MAO levels.

As Robinson and Niles (p. 298) point out, despite its general stability, platelet MAO activity can be altered by drugs. Some antidepressants and antihypertensive drugs have as their major mode of action the production of markedly reduced MAO activity in all tissues (including platelets). The question has been raised as to whether other drugs, not widely recognized as specific MAO inhibitors, might also reduce the activity of the enzyme to some extent. This could be by some direct action or even by an indirect effect such as altering platelet volume or protein content, as discussed by Friedhoff and Miller (p. 314). Since most schizophrenics have been treated with neuroleptics at some time in their lives before they enter a research sample, resolution of this problem is an important research issue (see Wyatt and Murphy 1976) but relatively intractable. Neuroleptic effects could be held to be very long lasting and easily triggered by only a few doses of drug, effectively eliminating nearly every diagnosable schizophrenic from a research sam-
people. Untreated schizophrenics might be argued to represent a special subsample of milder or unusual psychosis, not truly chronic (hence low MAO type) schizophrenia. High risk strategies using nonpatients and family studies, as discussed by Haier (p. 334), Puchall (p. 338), and Berrettini (p. 235) and their co-workers, are an attempt to circumvent this problem.

Finally there is generally fairly high stability of MAO levels across time in normals and in patients. Murphy et al. (1977b) measured MAO activities in chronic schizophrenics and unipolar depressed patients over a 2-year period and normals over 2 months, while Carpenter, Murphy, and Wyatt (1975) studied acute schizophrenics over 1 year. Only 15 to 20 percent changes over time were found in all of these groups.

This intraindividual stability is seen across time and across marked changes in clinical state, including acute and severely psychotic episodes. MAO levels in schizophrenic patients are seemingly unaffected by changes in physical activity, dietary intake, sleep, drug treatment, and remission (Carpenter, Murphy, and Wyatt 1975; Murphy et al. 1977b) and the same is true of cycles of severe mania and depression in bipolar patients (Murphy and Wyatt 1975). Thus, it is difficult to interpret suggestions that short-term changes in MAO activity levels might be related to changes in clinical symptoms (Becker and Shaskan 1977). It would seem more likely that MAO activity might represent a stable factor which interacts with environmental changes to result in psychological differences. One interesting but unproven environmental factor could be dietary loads of some amino acids such as tryptophan, with low MAO individuals showing unusual metabolic patterns (see Domino, p. 238).

Are MAO Activities Under Genetic Control? Because both schizophrenia and bipolar affective disorders seem to be under partial genetic control, the question arises about blood platelet MAO activities. Despite the large amount of evidence supporting genetic control of MAO (well reviewed by Berrettini et al., p. 235, and Breakefield and Edelstein, p. 282), the pattern of inheritance cannot be reduced to a dominant or recessive single gene locus. Breakefield and Edelstein approach the problem by noting the need to evaluate MAO types A and B separately, to investigate genes coding enzyme subunits, co-factors, MAO degradation, and to establish a molecular basis of variation in MAO level.

Are Blood Platelet MAO Activities Related to Neuronal Transmission? This is a complex and extremely difficult question to evaluate because many mammalian species including mice, rats, cats, and some other common laboratory animals lack MAO activity in platelets (Paasonen and Solautunturi 1964) rendering many experimental approaches to this problem impossible. The complexity of this assumption can be made manifest by examining the issues involved in how platelet MAO activities relate to brain and other tissue MAO activities which are available to degrade synaptic transmitters in vivo. It is important to recall that MAO is only one small part of the total chemical chain and structural mechanisms that regulate synaptic transmission. Extremely low MAO activity, for example, may be compensated for or reacted to by a variety of feedback mechanisms in another part of the chemical chain.

In regard to even the most elementary question of whether there is a relationship between MAO activities measured in platelets and those measured in brain and other tissues of the same individual, no definitive answer is yet available. MAO is a complex enzyme, or more likely a family of enzymes, with two major forms (type A and type B) now recognized. Platelets contain MAO type B exclusively (Murphy and Donnelly 1977), whereas almost all other tissues contain mixes of the A and B types in varying proportions. It is interesting from an evolutionary viewpoint that MAO-A is the predominant form in most rodent tissues, including brain, while there is a higher proportion of MAO-B than MAO-A in human and subhuman primate brain (see Murphy and Kalin, p. 355, and Edwards, p. 275). Moreover, brain regions in rodents and primates differ in their proportions of MAO-A to MAO-B, as well as in total MAO activity. Methods for distinguishing MAO-A from MAO-B activity are not completely specific. In addition, nonneuronal elements in brain, including blood vessels and glial cells, also contain MAO activity as high as that found in neuronal cells grown in tissue culture. Techniques to separate neurons from glia are fairly crude. There are also many different types of neurons, many of which do not use the amines as neurotransmitters, and hence isolation of amine-containing neuronal elements that only contain MAO-B has not yet been accomplished. This level of complexity makes it highly unlikely that simple comparisons of platelet vs. brain MAO activity will prove to be readily interpretable, even if the difficulties in obtaining usable postmortem brain samples can be overcome. Because intravas-
cular coagulation occurs at the time of death, platelet samples need to be obtained some time before death, again adding to the difficulty of doing an MAO brain/platelet correlation study in man.

Despite the extreme difficulty in obtaining direct data relating platelet MAO activity to brain MAO, there are some indications that platelet MAO activity may serve as an index of MAO activity in other tissues, including brain. As reviewed by Murphy and Kalin (p. 355), MAO-inhibiting drugs affect MAO-B activity in platelets and brain to a similar extent, and treatment with these drugs in animals and man leads to behavioral changes as well as other biochemical and pharmacologic effects which are interpretable consequences of the interruption of amine degradation by the inhibitors.

Are There Stable, Replicable Correlations of MAO With Psychological Expression? For the most part, studies of human MAO activity have sought to establish a relationship between MAO and a diagnostic category, in the hope that MAO is etiologically relevant to the fundamental symptoms of these categories. However, a close logical examination of this hypothesis in its simplest form (low MAO activity causes diagnoses x and y) suggests that MAO cannot be the main cause of all the fundamental symptoms of the two diagnoses of bipolar affective illness and chronic schizophrenia. While one frequently finds loose associations in both, it is hard to reconcile the notion that low MAO activity in isolation from other factors could be responsible for the elation of mania and the anhedonia in schizophrenia, the social aggressiveness of mania and the social withdrawal of schizophrenia, the sensation seeking quality of mania and the stimulus withdrawal in chronic schizophrenia. The above suggests that MAO research, having established some type of relationship of MAO with schizophrenia, and perhaps affective disease and alcoholism as reviewed by Belmaker, Bracha, and Ebstein (p. 320), needs to become much more analytic in its investigation of biochemical-psychological relationships. This simplified hypothesis needs to be made more complex and sophisticated at the biochemical-neurophysiological end as well as at the behavioral-psychological end.

Because blood platelet MAO activity ranges along a continuum, it seems reasonable to suppose that its psychological expression would be a continuum. And because MAO activities are normally distributed (Buchsbaum and Rieder 1979; Murphy et al. 1976), and most values lie within normal boundaries, then most of the range of psychological expression of MAO should be nonpathological. Indeed, many such normal correlates have been found. The dimensions that have been most replicated seem related to the person's disposition to seek stimulation in the outside environment. Examples of this theme include correlation of low MAO values with high scores on the Sensation Seeking Scale (Murphy et al. 1977a; Schooler et al. 1978); increased social interaction in both humans (Coursey, Buchsbaum, and Murphy 1979) and monkeys (Redmond, Murphy, and Baulu 1979); cigarette usage (Coursey, Buchsbaum, and Murphy 1979; Irving et al., in preparation) and drug usage (Coursey, Buchsbaum, and Murphy 1979; Stillman et al. 1978); greater activity and play in monkeys (Redmond, Murphy, and Baulu 1979); a tendency toward more stimulating leisure-time activities in man (Schooler et al. 1978); and psychopathic traits and legal convictions (Buchsbaum, Coursey, and Murphy 1976). Adler et al. (p. 226) extend the study of personality traits into psychiatric populations and report a consistent association of high platelet MAO with social introversion.

MAO correlates with the above dimensions across the whole central range of MAO values. Nevertheless, at the extremes of this MAO continuum, there may exist some specific relationships to more pathological states, like mania. Thus, groups of subjects with extremely high MAO activity levels have been found to have negative affect; social introversion and depression-related diagnoses (see articles by Puchall and Adler and their co-workers on p. 338 and p. 226).

On the other hand, extremely low MAO males have been found to have higher involvement with mental health treatment (Buchsbaum, Coursey, and Murphy, 1976; Coursey, Buchsbaum, and Murphy, in preparation; Irving et al., in preparation), suicide (Buchsbaum, Coursey, and Murphy 1976; Buchsbaum, Haier, and Murphy 1977), chronic schizophrenia (see reviews Wyatt and Murphy 1976; Wyatt, Potkin, and Murphy 1979), bipolar affective disorders (Leckman et al. 1977; Murphy and Weiss 1972), and alcoholism (Major and Murphy 1978; Sullivan et al. 1978, 1979; Wiberg, Gottfries, and Orelad 1977).

The area in which most of the studies have been done, the relationship of MAO activity with diagnostic categories, bears special scrutiny because a diagnostic category consists of multiple psychological traits and behaviors as well as physical and psychological consequences of the essential dysfunctions, combined
with adaptive coping efforts and defenses against the ravages of the disorder, all embedded in a psychosocial context (e.g., institutionalization; Mednick and McNeil 1968) which further shapes the diagnostic picture. Thus, a relationship between some level of MAO activity and this physio-psycho-social conglomerate, upon closer inspection, must mean a relationship with some one or several aspects of the diagnosed person's psychological state; and thus the biochemical variable cannot be automatically assumed to have etiological significance. It seems plausible that MAO activity could be related to any of six aspects of a diagnosed person's state. For purposes of this article, we will examine the relationship of MAO with the diagnosis of chronic schizophrenia.

First, MAO might be related to a central deficit such as loose associations (Coursey, Buchsbaum, and Murphy, in press) or attentional difficulties (Buchsbaum et al. 1978). However, this cannot be an exclusive association with the critical components of schizophrenia alone because low MAO activity is also associated with sensation seeking behavior, which at face value does not seem compatible with chronic schizophrenia (Schouler et al. 1978). Moreover, the low level of MAO found in some schizophrenics is a statistical rather than an absolute difference, and there are instances of high MAO among subjects carrying diagnoses of chronic schizophrenia (Schildkraut et al. 1978) and mania (Puchall et al. 1980). Proposed explanations include the suggestion that MAO may dis inhibit or facilitate, either biochemically or psychologically, some other fundamental etiological factor. For example, it is quite possible that the stimulant effects of low MAO might be so stressful to a schizophrenia-prone person as to stimulate hallucinations (see Adler et al., p. 226). In a similar vein, the weak relationship of MAO and diagnosis may be due to the fact that schizophrenic dysfunction results from the interaction of MAO with other variables; for example, with the physiological dimensions of augmenting-reducing (Coursey, Buchsbaum, and Murphy, in press; Haier et al. 1980), dopamine-beta-hydroxylase (Buchsbaum et al. 1978), cell membrane transport characteristics (Shaughnessy et al. 1980), or other not yet examined defects such as galvanic skin resistance (GSR) factors (Mednick and McNeil 1968; Salzman and Klein 1978) or brain damage (Goldstein 1978; Mirsky 1969). Finally, the relationship may not be due to a linear correlation with MAO at all, but simply the extremity of the deviation may set in effect other mechanisms which result in schizophrenia (Coursey, Buchsbaum, and Murphy, in press; Haier et al. 1980; Irving et al., in preparation).

A second possible explanation of the MAO-diagnosis connection is that MAO may not be related either directly or indirectly to some fundamental psychiatric symptom, but rather to a subsidiary, related phenomenon. This is suggested by the fact that while reduced MAO activities have been rather consistently found in chronic schizophrenia, in a number of studies of acute schizophrenia MAO showed little or no reduction (Carpenter, Murphy, and Wyatt 1975; Meltzer and Stahl 1974). Thus, MAO may be related to some factor producing chronicity rather than directly to classical schizophrenic symptoms. Shaskan and co-workers (p. 347), for example, hypothesize a link between MAO levels and host factors in viral infectious disease.

A third possibility is that MAO may be related to some third factor which is commonly associated with the diagnosis, but not of any etiological significance, such as treatment effects, associated addictive behavior, etc. Belmaker, Bracha, and Ebstein's (p. 320) hypothetical example of the fat college student having poor social adjustment and abnormal platelets secondary to his obesity is such an instance. A further example might be the possibility that long-term exposure to neuroleptics lowers platelet MAO (as is required for tardive dyskinesia). However, the possibility that this completely explains the clinical reports of low MAO in psychiatric illness seems remote because of the high correlation of MAO levels in first-degree well relatives of patients and in monozygotic twins discordant for schizophrenia (Leckman et al. 1977; Wyatt et al. 1973), as well as the association of low MAO with psychopathology in individuals untreated and undiagnosed (Buchsbaum, Coursey, and Murphy 1976).

Another way in which MAO activity might appear related to psychopathology would be through some mediating variable, such as alcoholism in affective disorders or smoking in chronically institutionalized patients. Belmaker, Bracha, and Ebstein (p. 320) review the studies finding low platelet MAO activity related to alcoholism, and Adler et al. (p. 226) report the same association within a group of hospitalized psychiatric inpatients. It thus might be the higher incidence of alcohol usage in affective disorders which could be responsible for low MAO activity rather than a direct relationship of MAO activity and affective disorders. In these alcoholism studies, the group comparison methodology was unable to rule out...
the possibility that alcoholic consumption might reduce MAO activity rather than that low MAO levels constitute a predisposition to alcoholism. However, the results of Puchall and co-workers (p. 338) decrease the likelihood that alcohol causes the low MAO levels observed in alcoholics because this study identified people at risk for alcoholism on the basis of probands who had low MAO activity levels but were not alcoholic themselves. A similar question might be raised about the low MAO activity found in 26 marijuana smokers when compared to nonsmokers. However, no acute reduction in MAO was found following smoking a marijuana cigarette containing 15 mg of delta-9-tetrahydrocannabinol (THC), nor did THC inhibit MAO activity in vitro concentrations greatly exceeding in vivo plasma concentrations (Stillman et al. 1978). These studies suggest that lowered MAO activity is not a consequence of these addictions and thus open the door to a possible relationship of MAO and the addiction-prone personality.

A fourth possible explanation of the MAO-diagnosis relationship is that reduced MAO levels are a consequence of the disorder rather than the cause. Psychiatric patients might exercise less or consume unusual diets affecting monoamine metabolism. However, low MAO levels have not been found in hospitalized controls, and control of dietary monamines has not affected platelet MAO. Another possibility is that changes in MAO activity may be a consequence of behavioral activity or cortical or autonomic arousal, rather than a cause. If so, one would expect this arousal to be a nonspecific stress which might effect other biochemical changes, such as norepinephrine, which in turn might affect MAO levels (Gentil, Greenwood, and Lader 1975) or cortisol. Neither norepinephrine nor cortisol have reliably differentiated schizophrenics or controls with anywhere near the limited success of MAO.

A fifth possibility is that MAO might be related to some traits such as sensation seeking, disinhibition of impulse control, and/or rule-breaking that negatively affect the patient’s environment and social support system. Thus, these traits could call attention and concern to persons disturbed by a variety of biological and/or psychosocial factors which, in turn, would facilitate his entering the mental health system and receiving a psychiatric diagnosis and treatment. In several studies (Buchsbaum, Coursey, and Murphy 1976; Coursey, Buchsbaum, and Murphy, in preparation; Irving et al., in preparation), low MAO subjects had seen a psychiatrist but were not presently diagnosable. Or these MAO-related traits may simply create stressful situations (e.g., divorce, jail terms) which precipitate breakdowns in vulnerable persons.

Finally, extreme MAO levels may be a marker for vulnerability to psychiatric illness (Murphy and Buchsbaum 1978; Post and Murphy, in press) and may be unrelated to whether the person is merely predisposed, severely psychotic, or in remission. The evidence that supports this possibility was discussed above under the stability of MAO activities within individuals.

**Three Research Methodologies for Use With MAO: Their Pitfalls and Problems**

**Psychopathological Group vs. Normal Control Strategy.** The overwhelming majority of the studies investigating the psychiatric relevance of MAO activity have used the traditional biochemical research paradigm of comparing the assays of a pathological group (e.g., schizophrenia, affective disorders) with a control group. The methodological difficulties with this approach to biochemical differences have been well documented elsewhere (e.g., Bannister 1971; Kety 1959; Mednick and McNeil 1968; Post and Murphy, in press). But in order to understand the rationale for making the independent variable biological rather than psychiatric diagnoses, we need to enumerate some fundamental strategic difficulties in four areas with this basic research strategy.

The first set of problems centers on the selection criteria for the pathological group. Beyond the problems of establishing clear and reliable categories (e.g., Buchsbaum and Haier 1978; Falek and Moser 1975) with symptomatic homogeneity, particular problems arise in using a disease category method in neurochemical investigations of psychological disturbances. The disease model makes most sense when there is some clear abnormality, trauma, or pathogen, and when the symptoms are themselves directly traceable to its pathophysiology. Trauma and pathogens suggest a disjunctive, qualitative difference between health and disease, and diagnostic categories make sense in that context. But many of the neurochemical, physiological variables studied, such as MAO, dopamine-beta-hydroxylase, and evoked potentials, are continuous and normally distributed. Also it is quite unlikely that an experiential category, defined without regard to a biological substrate, based primarily on language and social phenomena, would correspond
even roughly with some underlying biochemical abnormality. Even if a group of subjects were perfectly homogeneous with respect to psychiatric symptoms, there is no guarantee that they would be homogeneous with respect to etiology. Indeed, most researchers assume biological heterogeneity in schizophrenia and in affective disorders (e.g., Bellak 1979; Buchsbaum and Haier 1978; Buchsbaum and Rieder 1979; Kraepelin 1968; Murphy and Buchsbaum 1978; Sullivan 1947). Given such a situation, Buchsbaum and Rieder (1979) have demonstrated through a computer simulation the low probability of finding and replicating biological differences when only a certain percentage of the pathological group has a particular biological etiology.

The second major deficit for this model is establishing an adequate control group which is equivalent on all other relevant dimensions (such as the effects of long-term stress, institutionalization, diet and habits of hospitalized patients, subtle accompaniments such as mild brain damage, etc.).

The third area is untangling essential biological factors from other interactive factors and artifacts. This method simply is unable to sort out a principal biological factor from other relevant, interactive, or irrelevant but concomitant biological and environmental variables. For instance, any attempts to examine family and stress variables in the group comparison strategy must be retrospective, and thus subject to considerable bias (Fontana 1966). Further, one cannot establish the power of a particular biological factor because of these confounding effects. Moreover, etiologically significant variables cannot be distinguished from disease or treatment consequences. Now that we know some of the long-lasting side effects of pharmacological treatment (e.g., tardive dyskinesia) we must also worry about permanent biochemical alterations due to past treatment.

Finally, there is the danger of false attribution. Even if one could definitively prove a relationship between MAO and diagnosis, and rule out all artifacts, one cannot conclude that the specific symptom constellation is caused by this biological factor. The psychological expression of the same biological factor may vary according to environment, learning, coping and defenses, intelligence, culture, and other biological variables. Extreme MAO activity, as pointed out above, may simply be a general mental health vulnerability factor or a genetic marker.

**Longitudinal High Risk Research.** In its most common form, this research approach establishes the high risk group on the basis of a psychiatric diagnosis of the mother, and then the children are periodically assessed over a 15-20 year period (Mednick and McNeil 1968). As outlined by Mednick and McNeil (1968), it has many desirable features, including excellent procedures for establishing control groups. It also helps untangle the antecedents from the consequences of the disorder, but cannot establish the direct relevance of any of the biological and psychological differences uncovered, nor the power of these factors. Moreover, its basic procedure for establishing the high risk group still depends on phenomenological diagnoses, with their attendant problems mentioned above.

**Biological High Risk Research.** A biological high risk method (Buchsbaum, Coursey, and Murphy 1976; Buchsbaum and Rieder 1979; Coursey, Buchsbaum, and Murphy 1979) suggests an alternative to the usual subject selection strategy. Instead of using psychiatric diagnosis of mother as an index of risk and then looking for differences in biological and psychological variables in the offspring, one could define the subjects in the high risk group solely on the basis of some hypothesized deviant biological variable. This method has a number of advantages over previous forms of high risk research. First, it tests explicit hypotheses about a biological variable and its psychological correlates, and also gives some indication of how potent that variable is in relationship to other vicissitudes of living. Second, it avoids the problem of biological heterogeneity (Buchsbaum and Rieder 1979) and lack of reliability of psychiatric diagnoses. Third, it requires the researcher to explore the hypothesized psychological expression of the biological variable in the normal as well as pathological range.

This model also has drawbacks. While it allows adequate control groups, much of the adequacy of the controls is based on randomization found in the normal population. For instance, differences in psychopathology found in the Coursey, Buchsbaum, and Murphy study (1979) were attributed to MAO activities rather than to family variables, because the random selection procedure is presumed to have eliminated systematic biases in the families. But child-parent correlations of MAO activity levels, as well as increased levels of psychopathology among parents of children possessing extremes of MAO activity (see Puchall et al., p. 336), make disentangling biology from modeling and family interactions still impossible without adopted-away studies.
Thus far, control groups have been established primarily on the basis of their MAO values, although age, education, socioeconomic variables, and sex were equivalent. In light of the common reports of different mean MAO values between males and females (Buchsbaum, Coursey, and Murphy 1976; Murphy and Weiss 1972; Murphy and Wyatt 1972; Murphy et al. 1977a; Robinson et al. 1971) and the reversal of some effects on the basis of sex (Coursey, Buchsbaum, and Murphy, in press; Murphy et al. 1977a; Puchall et al. 1980), analysis of data separately for men and women is important. The first control group used in this type of research had extremely high MAO levels. They were selected in the hope that extreme deviations would enhance the likelihood of finding MAO effects and because psychopathology had not been found related to high MAO activity. Subsequent reports have found predictable adjustment problems in these high MAO groups (Irving et al., in preparation; Puchall et al. 1980; Schildkraut et al. 1978). Consequently, a middle MAO group is now being used for comparison with the extremes (Irving et al., in preparation).

Pedigree Studies. With conventional pedigree studies, it has been difficult to identify a single gene locus for schizophrenia. As Elston and Namboordiri (p. 368) point out, narrowing the groups examined to those who have a specific biological abnormality may be helpful in reducing heterogeneity. Patients with a particular biological abnormality are selected as probands, and then their relatives are examined. If the biological abnormality is of significance, in this patient subgroup, then their psychiatrically ill relatives should also have the biological abnormality. Application of this strategy to schizophrenia is a critical next step.

Psychotropic Drug Response as a Subgroup Criterion. This third strategy involves the use of drug response as the independent variable and examining MAO level as the dependent variable. This approach is reviewed by Murphy et al. (1978b) and seems especially appropriate for MAO inhibitor studies where individual differences in response seem so prominent.

Summary

Reviewing the contributions to this conference cannot but leave the reader impressed, if not with the clinical findings, at least with the importance of monoamine oxidase in the neurochemical economy to the central nervous system. Instead of the question “Do schizophrenics have low MAO?” one might reverse the question “How can a brain with low MAO work at all?” This new way of posing the question may be the more powerful. Freed of the question “What is a schizophrenic?” whose answer is ambiguous in the face of the absence of a widely agreed upon external validating criterion for current diagnostic systems, the biological researcher can use a biological strategy. It focuses the approach on the biological measure for which the tools for measurement validity are more certain than those for psychiatric diagnoses. It broadens the behaviors under study so that new symptoms, deficits, and even strengths can be part of the low MAO syndrome. And lastly, because it begins with a neurochemical abnormality, it is more likely to lead to the identification of individuals for whom specific neurochemical interventions will be effective.

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