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EDITORIAL

The lessons of platelet monoamine oxidase[1]

Over a decade has elapsed since the first report by Murphy & Wyatt (1972) that platelet monoamine oxidase (MAO) is reduced in chronic schizophrenic patients. The finding was exciting because it seemed to herald a new, more scientific level of research on the biological aspects of schizophrenia. Previous claims in schizophrenia of altered serum factors (Heath *et al.* 1958), of elevated serum creatinine phosphokinase (Meltzer, 1968), or of abnormal urinary metabolites (Friedhoff & Van Winkle, 1962) had never been entirely proven or disproven. However, such findings tended to be isolated from comprehensive theories of schizophrenia and unrelated to neuroleptic treatment, the major effective biological treatment of schizophrenia. Reduced MAO seemed logically to be an aetiological factor in schizophrenia, for MAO metabolizes dopamine, and MAO deficiency would predispose to dopamine excess. Dopamine excess had been proposed as a pathophysiological basis for the overt symptoms of schizophrenia (Carlsson *et al.* 1972), and neuroleptics had been shown to act as dopamine receptor blockers (Snyder *et al.* 1970). MAO is an enzyme, and biological theory in 1972 was much preoccupied with the 'central dogma' that genes express themselves by determining the amino acid sequence of particular proteins that are the products of the gene (Watson, 1965). Rosenthal *et al.* (1971) had just published their influential adoption studies of schizophrenia that helped to reverse the highly sceptical attitudes of North American psychiatrists towards the issues created by the methodological difficulties associated with previous genetic studies in the field of schizophrenia.

Low platelet MAO in schizophrenia was therefore viewed as the possibly enzymatic expression of the genetic predisposition to schizophrenia. It was an admission ticket for psychiatric research to the great arena of molecular genetics, the forefront of modern biology. Moreover, it seemed possible to create a molecular biology of schizophrenia without sacrificing psychiatry's legacy of biological–psychological interactions. Low MAO could only represent the genetic *predisposition* to schizophrenia. Under usual conditions MAO is present in great excess and a relative deficiency would not affect dopamine metabolism (Murphy & Kalin, 1980). Other, presumably environmental, causes would be necessary to stimulate a dopamine release that might become a pathological dopamine excess 'psychosis' in an individual with low MAO. Neuroleptic or dopamine receptor blocking drugs could be seen to reduce the effects of dopamine excess and thereby ameliorate schizophrenic symptoms, while leaving unaffected the low platelet MAO and the genetic predisposition to further attacks (Wyatt *et al.* 1975).

In the early 1970s the implications of the finding of low platelet MAO in schizophrenia were exciting indeed to young psychiatric research workers at the National Institute of Mental Health, the author of this editorial among them. The heuristic result was an explosion of empirical studies. Nies *et al.* (1973) had already shown, in a comparison of normal monozygotic and dizygotic twins, that interindividual differences in platelet MAO are under a high degree of genetic control, with a heritability of over 80%. Preliminary studies showed no effect of neuroleptic drug treatment on platelet MAO activity (Murphy *et al.* 1975). Yet it was, of course, possible that other factors such as hospital diet, stress, infection or inactivity could be artefactual causes of low platelet MAO in schizophrenia. It seemed an impossible task to eliminate each of these factors one by one. Basing himself on a strategy used extensively by Pollin (Pollin & Stabenau, 1968), Wyatt planned a study of monozygotic twins discordant for schizophrenia (Wyatt *et al.* 1974). Such twins are discordant for neuroleptic treatment history, for hospitalization effects, and for effects of stresses secondary

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to the schizophrenic illness. In 13 such pairs of twins, platelet MAO was found to be significantly correlated ($r = 0{\cdot}67$). The mean platelet MAO of the schizophrenic twins was not different from that of their genetically identical but non-schizophrenic co-twins ($\bar{X} = 4{\cdot}7$ *v.* $\bar{X} = 3{\cdot}9$). The mean platelet MAO of age- and sex-matched normal controls assayed with the discordant twins was $6{\cdot}4 \pm 2{\cdot}7$, significantly greater than platelet MAO in either the schizophrenic twins or their normal co-twins. These results seemed to present irrefutable proof that the reduction of platelet MAO in schizophrenia is a genetic predisposing factor present before the onset of illness, and not a biological artefact resulting from the illness or its treatment.

In retrospect, it appears that we overemphasized the value of this twin study and overlooked its methodological faults. The blood sampling of the schizophrenic subjects and their normal co-twins was generally carried out at their places of residence scattered over the USA; platelet isolation and storage were achieved under 'field' conditions. While some attempt was made to collect simultaneous normal controls near the subjects' residences, most controls were hospital staff, and platelet isolation was achieved under ideal laboratory conditions. The significant correlation between schizophrenic patients and their co-twins supports the technical accuracy of the platelet isolation and assay; however, a correlation of 0·67 explains less than half the variance and leaves much room for environmental or artefactual factors.

Attempts to replicate the finding of low platelet MAO in schizophrenia immediately led to mixed results. Meltzer & Stahl (1974) found low platelet MAO in schizophrenic patients using tyramine as the assay substrate, but no reduction if they used tryptamine, the original substrate of Murphy & Wyatt (1972). On arriving in Jerusalem in 1974, I undertook a replication, using diagnostic and biochemical procedures modelled after my personal experience at NIMH, and found non-significantly *increased* platelet MAO in a chronic schizophrenic sample compared with controls (Belmaker *et al.* 1976*a*). Reluctant to accept these data, we performed a study on a new sample of schizophrenic patients with at least one schizophrenic first-degree relative (Belmaker *et al.* 1977*a*). Again, no difference was found in platelet MAO compared with normal controls. Many other groups were, however, able to replicate the original finding. At the NIMH Conference on Schizophrenia and Platelet Monoamine Oxidase at Chevy Chase, Maryland, in September 1979, Wyatt reviewed 32 published studies (Wyatt *et al.* 1980). All but 6 found some decrease in platelet MAO activity in chronic schizophrenia and in 22 studies the decrease was statistically significant. Using a simple sign test, Wyatt suggested that such results indicate a statistically significant reduction in platelet MAO activity across all studies. Buchsbaum & Rieder (1979) proposed a computer simulation of research, given a heterogenous illness like schizophrenia which might be associated with low platelet MAO in only a fraction of all individuals. If sample sizes are 15–30 schizophrenics (as they usually are), and if low platelet MAO occurs in only one quarter or one half of all schizophrenic patients, then computer simulation reveals that a considerable proportion of research teams will miss a real finding, merely by chance. It should be realized that this strategy is inherently defensive, implying that the existence of some negative studies is not inconsistent with the truth of a statistical association. Other explanations, however, may also account for the existence of both positive and negative studies. For instance, 22 positive studies of the total of 32 reviewed by Wyatt may constitute a positive sign test, but 22 out of 44 is mere chance. Twelve absent negative studies could conceivably be due to a publication bias towards positive results.

Further studies of platelet MAO in schizophrenia continue to be carried out. While a box-score approach is probably not useful here, it is perhaps fair to say that two-thirds of the studies continue to find low platelet MAO in schizophrenia and one-third do not. It has been suggested (Belmaker *et al.* 1977*b*) that population genetic differences might be involved in these inconsistencies. For example, a research worker studying anaemia in East Africa would find an association with sickle-cell haemoglobin, but a research worker in Sweden would not. This line of thinking is again defensive and is more satisfying if one already believes in the importance of platelet MAO than if one does not. The sickle-cell anaemia analogy, however, was instrumental in stimulating a number of investigations of the molecular nature of platelet MAO in normal and pathological conditions. The underlying concept in these molecular studies is that a genetically-determined amino acid substitution

in the protein MAO molecule may reduce its activity, but might also affect its properties in other ways. Genetic mutations may affect affinity constants (Km), electrophoretic mobility, inhibition constants for various enzyme inhibitors, heat stability of the enzyme, etc.

One report suggested that the affinity constant of platelet MAO in schizophrenic patients was elevated (Belmaker *et al.* 1977*b*), implying decreased affinity, but other groups reported the opposite – reduced affinity constant of platelet MAO in schizophrenia (Kobes *et al.* 1979). Amphetamine inhibition constant was studied because of the sensitivity of schizophrenic symptomology to exacerbation by amphetamine and was found to be normal (Reches *et al.* 1977). Electrophoretic mobility of platelet MAO from schizophrenic patients was found to be no different from that of normals (Belmaker *et al.* 1976*b*). The possible existence of a circulating MAO inhibitor in the plasma of schizophrenic patients has also been considered and studied empirically. While Berrettini & Vogel (1978) found evidence for the existence of such a factor, other groups could not replicate these results (Wise *et al.* 1979).

The existence of so many statistically significant results that are not replicated in other laboratories tends to undermine belief in the value of statistical methods. Perhaps the harshest blow to the claim that low platelet MAO predisposes to schizophrenia was the finding that brain MAO is *not* reduced in schizophrenia (Crow *et al.* 1979; Eckert *et al.* 1980; Schwartz *et al.* 1974). Autopsy studies have examined MAO in many brain regions of deceased schizophrenic patients and have differentiated Type A and Type B MAO pharmacologically. No reduction was found in any area of any type of MAO. Moreover, MAO is not an enzyme that disappears rapidly after death (Fowler *et al.* 1980) and there is little reason to suspect post-mortem artefacts in these studies. Evidence that platelet MAO might reflect brain MAO *somewhere* in the brain was provided by the work of Kleinman *et al.* (1979), who reported a strong correlation between platelet MAO activity and plasma prolactin, a hormone controlled by hypothalamic dopamine. However, Baron *et al.* (1983) could not replicate the correlation.

If brain MAO is not reduced in schizophrenia, what could be the meaning of the preponderance of studies showing low platelet MAO in schizophrenia? Neuroleptic treatment, the old contaminant of findings in biological psychiatry, may be the culprit. Early evidence against neuroleptic effects (Murphy *et al.* 1975) and early data on the high heritability of platelet MAO activity were too easily accepted. Several recent investigators (Chojnacki *et al.* 1981; De Lisi *et al.* 1981; Owen *et al.* 1981; Sahai *et al.* 1981) have reported neuroleptic-induced declines in platelet MAO. The effect is not immediate and may be limited to some specific neuroleptic drugs; thus this effect could possibly explain why some populations of schizophrenics show low platelet MAO and others do not. Animals other than primates do not have MAO in platelets, and so the question has not been easily amenable to animal studies.

An important reason for an editorial of this type in a general psychiatric journal such as *Psychological Medicine* has not yet been mentioned. It is that platelet MAO has become much more than a 'finding' in schizophrenia. In 1972 Murphy & Weiss had already published work suggesting that bipolar manic-depressives have reduced platelet MAO, although not as markedly as in schizophrenic patients. Genetic overlap between the two illnesses was advanced as a possible explanation (Murphy *et al.* 1975). Based on the concept of the schizophrenia spectrum, Murphy *et al.* (1977) studied correlations of platelet MAO with personality variables in normal male and female young volunteers. Several correlations reached statistical significance in a univariate model and were also in the expected direction. For instance, the disinhibition score on the Zuckerman Scale (Zuckerman, 1978) was correlated in males only ($r = -0{\cdot}51$) with platelet MAO: that is, the lower the platelet MAO, the higher the disinhibition score. This was an exciting preliminary study, consistent with the view that personality traits exist on a continuum with psychopathology. Clearly, a true 'genetic marker' in schizophrenia would be present in at least several per cent of the normal population, since monozygotic concordance rates for schizophrenia are less than 50% (Rosenthal, 1970). At least as many persons genetically identical to schizophrenics are psychologically non-schizophrenic. Such persons might be expected to exhibit personality markers of their genetic vulnerability to schizophrenia, and these personality markers in the general population should

therefore correlate with possible biochemical markers of the vulnerability to schizophrenia. Rosenthal *et al.* (1971) found an increased incidence of severely psychopathic personality and suicide in the adopted-away relatives of schizophrenic patients; it therefore seemed promising to evaluate platelet MAO throughout the 'schizophrenic spectrum' of related psychiatric disorders. Indeed, numerous reports now claim low platelet MAO in alcoholism (for review, see Belmaker *et al.* 1980), and even in persons at risk for viral infections (Shaskan *et al.* 1980). In surveying this literature, it is important to realize that the original study (Murphy *et al.* 1977) examined over 100 simultaneous Pearson correlations: 21 were significant at the 0·05 level; none was significant at the 0·01 level. There were many significant correlations of personality with plasma MAO, an entirely different enzyme unrelated to mitochondrial MAO in platelet or brain (Gershon *et al.* 1977). Plasma MAO is most probably related to collagen metabolism or liver disease (McEwen, 1972), and correlations of plasma MAO with personality variables should have warned us of the probability of artefact.

A methodological development of the personality and platelet MAO correlations was the 'biochemical high risk paradigm'. In this promising study, Buchsbaum *et al.* (1976) measured platelet MAO in 375 college students and university employee volunteers. The top and bottom 10% in platelet MAO were then contacted for psychosocial study. Low MAO subjects reported a twofold higher incidence of psychiatric contact than high MAO subjects. Three past psychiatric hospitalizations were found in the low MAO group and none was found in the high MAO group. Relatives of low MAO males had an eightfold increase in the rate of suicide or suicide attempts compared with relatives of high MAO males. These data, combined with the high heritability of platelet MAO differences between individuals, suggested that platelet MAO may be a genetic marker for vulnerability to several psychiatric disorders, or a biological marker of pathogenic personality traits. The methodology of the biochemical high-risk strategy has been described as 'powerful' and 'ingenious', but it may be important to realize that these are not synonyms for 'foolproof' or 'definitive'. Indeed, Propping *et al.* (1981) attempted a replication of the study of Buchsbaum *et al.* (1976) with negative results: they studied 383 healthy students, attempting to correlate platelet MAO with several personality measures, but found no differences between the 10% of students with highest and lowest platelet MAO.

Perhaps these negative data regarding platelet MAO as a genetic marker in psychiatric disorder would be less surprising if we substituted the words 'serum cholesterol' for 'platelet MAO'. Serum cholesterol is under a high degree of genetic control, yet environmental factors can still have a major impact on serum cholesterol levels between groups. Correlations exist between serum cholesterol and behavioural measures, yet no-one would suggest that serum cholesterol is a genetic marker for the vulnerability to certain behavioural traits. Serum cholesterol levels, instead, may be a peripheral biochemical result of behaviour involving diet and stress. If we can suspend excessive respect for MAO as an enzyme and thus as a gene product, the parallel becomes clear. Platelet number and platelet subtypes and platelet mitochondrial density may also respond to stress, to dietary habits and to life style, so that platelet MAO may correlate with behavioural measures for very mundane, even artefactual reasons. Platelet MAO may be a variable with behavioural and genetic correlates, but it is not the golden path to the molecular biology of the mind. It is another peripheral variable like serum cholesterol, and must be taken down from the pedestal of molecular genetics.

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