

Demographic, Biologic, and Other Variables Affecting Monoamine Oxidase Activity

by Donald S. Robinson and Alexander Nies

Abstract

Monoamine oxidase (MAO) activity has been shown to be influenced by a variety of demographic, biologic, and other variables. Human platelet, plasma, and brain enzyme activities correlate with age and are higher in women. Brain catecholamines tend to decrease with age. The acute effects of ethanol on platelet MAO do not appear to be significant, but chronic ethanol ingestion could influence enzyme activity through a variety of possible mechanisms. Numerous drugs and hormones have been shown to alter platelet and tissue MAO. Heterogeneity of platelet size, density, age, and enzyme activity complicates the study of MAO in clinical populations. Newer platelet isolation techniques may diminish the variability due to platelet sampling. Studies of platelet MAO activity in schizophrenia require that careful attention be given to controlling for variables possibly influencing the blood enzyme activity, such as prior neuroleptic treatment. The limited studies of brain MAO activity in man fail to demonstrate differences between patients with schizophrenia and normal controls.

Since the introduction of an assay for monoamine oxidase (MAO) activity in blood platelets 10 years ago (Robinson et al. 1968), numerous and varied patient and normal populations have been surveyed for enzyme activity. There has been particular interest in the potential biologic significance of this platelet enzyme, especially in the affective disorders and schizophrenia, because of a body of indirect evidence suggesting that catecholamine metabolism and function may be altered in these disorders (Carlsson 1978; Murphy, Campbell,

and Costa 1978; Schildkraut 1978). Other lines of investigation employing this assay have examined the possibility of a meaningful relationship between platelet and tissue MAO (especially the brain and platelet enzymes) and monitoring MAO inhibition during treatment with phenelzine as a guide to therapy (Robinson et al. 1978).

Considerably more work needs to be done in all of these areas of interest, especially to establish if important relationships do exist between MAO activity as measured in the platelet and amine metabolism, either in the periphery or in the central nervous system. The demonstration of some relationship between platelet MAO activity and monoaminergic function would provide a physiologic rationale for utilizing blood platelet enzyme activity as a genetic marker for risk of psychiatric disorder, or as a useful index of pharmacologic effect and optimal dosage during drug treatment.

When platelet MAO studies were initiated, it rapidly became apparent that there is a large interindividual variation in both platelet and plasma MAO activity, with an 8- to 10-fold range in normals (Robinson et al. 1971). Similarly large variations have also been documented in man for other enzymes involved in monoamine pathways, i.e., plasma dopamine- β -hydroxylase (Markianos et al. 1976; Shopsin et al. 1972) and red blood cell catechol-O-methyltransferase (COMT; Cohn, Dunner, and Axelrod 1970). Various studies have been carried out to account for sources of variance of platelet MAO activity in normal and

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patient populations. Certain demographic, biologic, and pharmacologic variables have now been identified as contributing factors to the significant variability of human MAO activity and will be discussed here.

Relationship of MAO Activity and Age

In 1971 we reported a highly significant positive correlation between age and MAO activity in plasma and platelets of normal controls ranging in age from 20 to 80 years (Robinson et al. 1971). We also reported that MAO activity correlates positively with age in crude homogenates of human hindbrain obtained at autopsy from individuals who died from various accidental and medical causes (Robinson et al. 1972). Furthermore, in hindbrain, norepinephrine (NE) levels correlated negatively with both age and MAO activity.

In a subsequent study postmortem specimens from eight different brain areas were examined in a series of 38 individuals who died from various causes (Robinson et al. 1977). MAO activity measured with benzylamine and tryptamine substrates correlated positively with the age of the individual for each brain area. This age-MAO correlation was most significant in the nigrostriatal and hypothalamic regions, areas with very high catecholamine concentrations. Regional COMT and tyrosine hydroxylase activities bore no relationship to age of the individual. As in the prior hindbrain study, NE levels measured in hypothalamus and hippocampus showed significant negative correlations with age. There was also a consistent trend for the NE-age correlation to be negative in all areas. Other investigators have also reported increasing brain MAO

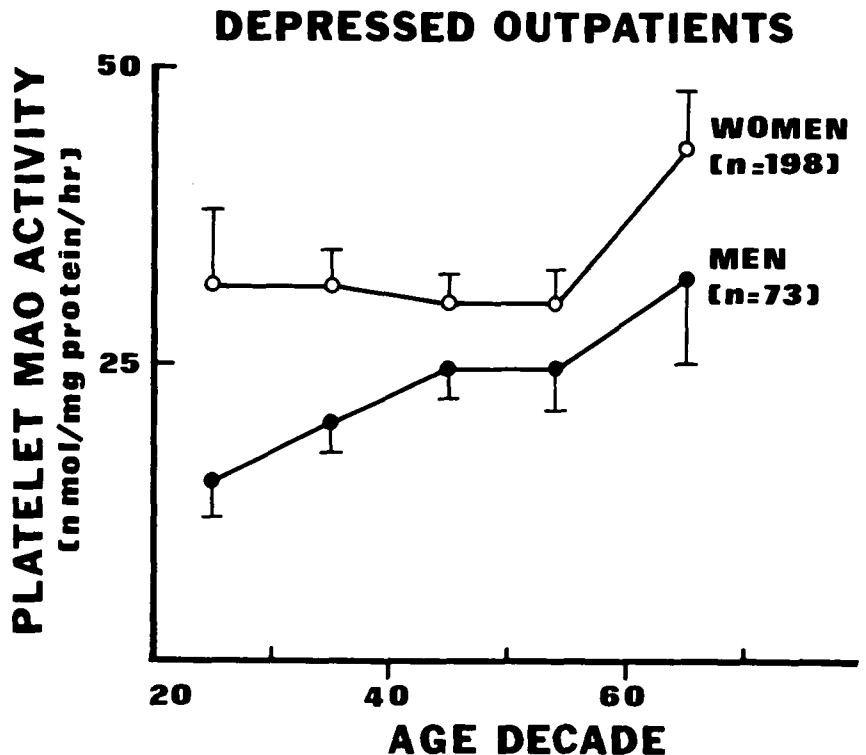
activity with aging (Gottfries et al. 1974, 1975; Grote et al. 1974).

A number of studies have confirmed significant age-MAO correlations for the plasma and platelet enzymes. Belmaker et al. (1976) and Mann (1979) have both reported a relationship of age and the platelet enzyme. Investigating several different patient populations, we have consistently observed positive age correlations of enzyme activity and age with saline-washed platelets as the source of the enzyme. This includes a sample of inpatients and outpatients with depressive illnesses (Nies et al. 1974) and outpatients before treat-

ment in a second large antidepressant drug trial still in progress. In the latter series (figure 1) the age relationship is most impressive in male patients. In female patients mean activity of the platelet enzyme remained relatively constant over the span of 20 to 50 years, with a subsequent increase in enzyme activity observed after age 60 (figure 1).

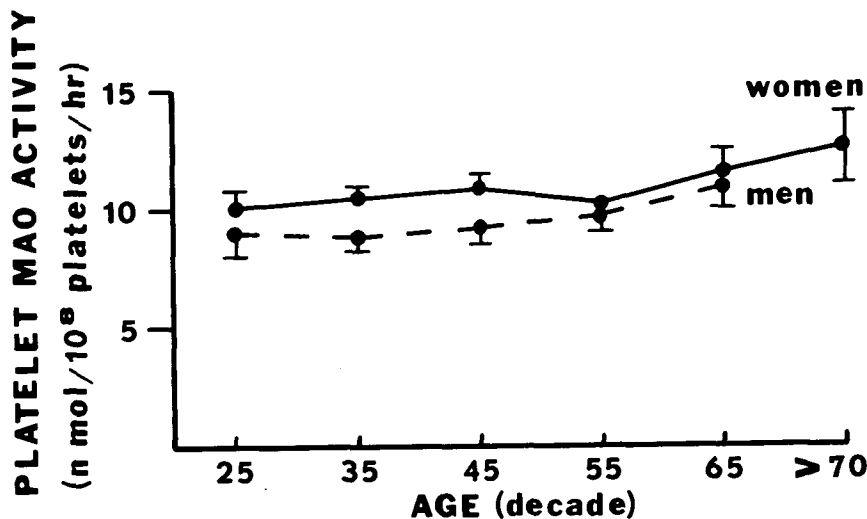
Platelet MAO activity was also measured in platelet-rich plasma in the depressed outpatients and expressed as nmole/10⁸ platelets/hr (figure 2). With this index of platelet MAO activity, a significantly positive age correlation and sex difference are

Figure 1. Mean platelet monoamine oxidase (MAO) levels by decade in male and female outpatients with depression



MAO activity of saline-washed platelets is expressed as nmole/mg protein/hr (\pm SEM) with benzylamine substrate.

Figure 2. Mean platelet monoamine oxidase (MAO) levels by decade in 48 male and 79 female outpatients with depression



MAO activity of platelet-rich plasma is expressed as nmole/10⁸ platelets/hr (\pm SEM) with benzylamine substrate.

again evident. Determined in this manner, platelet MAO activity does not show so marked an increase with age. A possible explanation for this discrepancy is the proportionately greater loss of dense high MAO platelets with the platelet-rich plasma method.

Increased plasma MAO activity with aging has also been noted (Robinson et al. 1971, Tryding et al.

1969). The functional significance of the plasma enzyme, a pyridoxal-dependent, soluble form of MAO, is not yet established.

Sex Differences in MAO Activity

In the study of 113 normal subjects (Robinson et al. 1971), women were found to have significantly higher mean platelet and plasma MAO ac-

tivity compared to men. Subsequently this sex difference was substantiated in depressed patients (Nies et al. 1974). Several other investigators have confirmed this finding (Belmaker et al. 1976; Murphy et al. 1976; Tryding et al. 1969).

Similarly, our studies of postmortem tissues have shown women to have higher mean brain MAO activity than men (Robinson et al. 1977). It appears that the sex difference in the platelet, brain, and plasma enzyme activities is a general phenomenon with important biologic implications. One could speculate that this sex difference in MAO activity is one etiologic factor in psychiatric disorders, in part accounting for, or contributing to, the greater prevalence of affective illness in women.

Other Physiologic Variables Affecting MAO

The reproducibility of the assay of platelet MAO activity with time has been assessed. Murphy, Belmaker, and Wyatt (1974) report a 6 percent variation in enzyme activity when assayed in platelets isolated from the same blood specimen, and a 17 percent variability within individuals sampled 1 week apart. This is consistent with our own experience with the platelet MAO assay. Therefore, more of the variance is attributable to the varied sampling of the heterogeneous population of platelets within a volume of blood as well as effects of time on platelet kinetics within an individual (as discussed, further below, and in accompanying articles in this issue).

We have examined short-term variability in six subjects (table 1). Using both benzylamine and tryptamine as substrates, with repeated sampling at 1½ and 3 hours, platelet and plasma MAO activity did not change

Table 1. Variability of blood MAO activity over time (n = 6 subjects)

	0 hr	1.5 hr	3.0 hr
Platelet¹			
Benzylamine	31.9 \pm 3.0	29.7 \pm 1.5	31.7 \pm 1.9
Tryptamine	2.6 \pm 0.5	2.1 \pm 0.4	2.3 \pm 0.4
Plasma²			
Benzylamine	16.2 \pm 1.0	16.0 \pm 1.1	16.1 \pm 1.4

¹ MAO activity expressed as nmole/mg protein/hr.

² MAO activity expressed as nmole/ml plasma/hr.

significantly over this time period. However, over a period of several months, some individuals will show a 15–20 percent variation in platelet MAO activity for unexplained reasons. This phenomenon may presumably be related to heterogeneity in platelet size, density, and enzyme activity and the sampling problem.

Platelet MAO activity fluctuates during the menstrual cycle (Belmaker, Murphy, and Wyatt 1974). In this study the variance attributed to the menstrual cycle was estimated to be 23 percent, with the peak MAO activity occurring during the ovulatory phase, followed by a nadir approximately 8 days later. In an earlier study we were unable to demonstrate a menstrual cycle fluctuation, presumably as a result of less frequent sampling during the interval (Gilmore et al. 1971). We also showed that there is a striking increase in platelet MAO activity in the immediate postpartum period, consistent with the well-described alterations in platelet kinetics in the early puerperium.

Plasma MAO activity is increased during the postovulatory phase of the menstrual cycle, and amenorrheic and postmenopausal women have been reported to have significantly higher plasma MAO activity than menstruating women (Klaiber et al. 1971).

Platelet MAO activity tends to be lower in patients with iron-deficiency anemia (Youdim, Grahame-Smith, and Woods 1976). This lower platelet enzyme activity associated with iron-deficiency anemia could be a reflection of altered bone marrow cell kinetics and platelet turnover or an effect of enzyme synthesis.

Although there is wide interindividual variation in platelet and plasma MAO activities, twin studies

have shown that there is a genetic component as one of the factors controlling the activity of these enzymes (Nies et al. 1973; Wyatt et al. 1973). Thus, inheritance plays some role in regulatory factors involving monoamine metabolism.

Among the many biologic variables that can be associated with differences in enzyme activity, racial and ethnic groups may be important and have not been adequately investigated.

Pharmacologic and Drug Factors Affecting Platelet MAO Activity

A variety of substances are now known to affect MAO activity as assayed in platelet preparations. We carried out a study of the effects of acute ethanol administration in eight normal subjects and found no significant changes in either plasma or platelet MAO (table 2). Subjects consumed sufficient ethanol over a 2-hour period to attain blood-alcohol levels in excess of 100 mg percent. Other investigators report low platelet MAO activity in chronic alcoholic patients (Wiberg, Gottfries, and Oreland 1977). Wiberg, Wahlström, and Oreland (1977) treated rats chronically with ethanol for 7 weeks, achieving blood levels between 140 and 690 mg percent without producing any significant changes in brain MAO activity. This discrepancy between ethanol effects on platelet and brain MAO is consistent with the possibility that chronic alcoholism, by producing changes in bone marrow and platelet kinetics due to one or more of several possible mechanisms (a direct toxic effect, iron and folate deficiencies, etc.), may affect platelet MAO activity measured in washed platelet and platelet-rich-plasma preparations.

Table 2. Effects of ethanol administration on blood MAO (n = 8 subjects)

	Control	Ethanol > 100 mg percent
Platelet¹		
Benzylamine	32.2 ± 1.4	29.1 ± 3.0
Tryptamine	2.1 ± 0.3	2.9 ± 0.3
Plasma²		
Benzylamine	14.6 ± 1.3	16.2 ± 1.2

¹ MAO activity expressed as nmole/mg protein/hr.

² MAO activity expressed as nmole/ml plasma/hr.

Two studies show that epinephrine administered subcutaneously produces an increase in platelet MAO activity (Bourne et al. 1976; Gentil et al. 1976). This rapid change in measured platelet enzyme activity within 90 minutes is more likely to be a result of a mobilization and "production" of circulating platelets secondary to epinephrine administration than a change in intrinsic enzyme activity of existing platelets. The effects of catecholamines on release of platelets into the circulation have been well documented (Harker and Finch 1969).

It has been reported that a siliconizing agent present in certain vacuum blood collection tubes can produce an inhibition of enzyme activity in platelet-rich plasma ranging from 30 to 49 percent (Pscheidt and Meltzer 1976). A variety of other substances and drugs are known to alter MAO activity *in vivo* as well (table 3). This list includes several competitive and noncompetitive inhibitors of MAO, the former being generally weak and reversible inhibitors *in vivo*, with little if any lasting effect on monoamine metabolism.

Table 3. Pharmacologic and other agents associated with altered MAO activity in *in vivo* studies

Decreased	Increased
Furazolidone ¹	Epinephrine ⁹
Debrisoquin, bretylium, guanethidine, etc. ²	L-Dopa ¹⁰
MAO inhibitor antidepressants ³	Corticosteroids ¹¹
Amphetamines ⁴	Lithium ¹²
Tricyclic antidepressants (high dose?) ⁵	
Nitroglycerin ⁶	
Insulin ⁷	
Alcohol (chronic?) ⁸	
Iron (deficiency)	

¹ Pettinger, Soyangco, and Oates (1968); Stern et al. (1967).

² Giachetti and Shore (1967); Kuntzman and Jacobson (1963); Pettinger et al. (1969).

³ Robinson et al. (1978).

⁴ Mantle, Tipton, and Garrett (1976).

⁵ Sullivan, Dackis, and Stanfield (1977).

⁶ Ogawa, Gudbjarnason, and Bing (1967).

⁷ Mosnaim et al. (1979).

⁸ Wiberg, Gottfries, and Orelund (1977).

⁹ Bourne et al. (1976); Gentil et al. (1976).

¹⁰ Tarver, Berkowitz, and Spector (1973).

¹¹ Ayitey-Smith and Kalsner (1977).

¹² Belmaker, Murphy, and Wyatt (1974); Bockar, Roth, and Heninger (1974); Mann (1979).

Brain MAO Activity in Schizophrenic Patients

Several investigators have assayed brain tissues obtained from schizophrenic patients at autopsy. These reports have uniformly failed to find a significant difference in brain enzyme activity compared to controls (Cross et al. 1977; Domino, Krause, and Bowers 1973; Nies et al. 1974; Owen et al. 1977; Schwartz, Aikins, and Wyatt 1974; Utena et al. 1968). The preponderance of evidence suggests that tissue (brain) MAO activity is not different in schizophre-

nia or the affective disorders. In a study (Robinson et al. 1977) of brains obtained at autopsy from subjects who died of acute accidental deaths or from suicide and from three pa-

tients with schizophrenia who died of acute medical causes, MAO activity was not depressed in the eight brain areas examined (tables 4 and 5). The somewhat higher activity in the

Table 4. Regional human brain MAO activities in schizophrenics and controls with benzylamine substrate¹

	Accidental deaths (n = 8)	Suicides (n = 2)	Schizophrenics (n = 3)
Mean age (yrs)	42	40	64
Brain area:			
Caudate	63 ± 7	45 ± 3	108 ± 32
Cortex	35 ± 4	25 ± 10	87 ± 21
Globus pallidus	40 ± 3	35 ± 7	77 ± 14
Hippocampus	43 ± 4	25 ± 3	87 ± 15
Hypothalamus	82 ± 11	69 ± 9	128 ± 15
Reticular activating system	50 ± 6	32 ± 1	91 ± 10
Substantia nigra	59 ± 7	38 ± 8	101 ± 5
Thalamus	45 ± 8	47 ± 6	127 ± 39

¹ Mean MAO activities with benzylamine substrate, expressed as nmole/mg protein/hr.

Table 5. Regional human brain MAO activities in schizophrenics and controls with tryptamine substrate¹

	Accidental deaths (n = 8)	Suicides (n = 2)	Schizophrenics (n = 3)
Mean age (yrs)	42	40	64
Brain area:			
Caudate	15 ± 1	13 ± 2	24 ± 4
Cortex	13 ± 2	12 ± 5	26 ± 4
Globus pallidus	10 ± 2	9 ± 3	23 ± 3
Hippocampus	14 ± 2	14 ± 2	27 ± 6
Hypothalamus	25 ± 2	28 ± 9	44 ± 9
Reticular activating system	14 ± 2	10 ± 2	32 ± 6
Substantia nigra	17 ± 2	13 ± 2	33 ± 1
Thalamus	14 ± 2	18 ± 1	35 ± 9

¹ Mean MAO activities with tryptamine substrate, expressed as nmole/mg protein/hr.

schizophrenic patients was presumably due to the increased ages of these patients.

Heterogeneity of Human Platelets and MAO Activity

Several studies have now documented the marked variation in size, shape, and enzyme activity of platelets, attributable in part to the age of circulating thrombocytes (Karparkin 1969; Karparkin and Sharmatz 1969). This has led to more recent attempts to develop experimental methods for more complete isolation of platelets, especially megathrombocytes (Karparkin 1978). Several studies have now shown that nongenetic factors, such as changes in platelet number, volume, and protein content, which may be associated with various forms of stress, iron and vitamin deficiencies, and drug effects, could affect the specific activity of platelet MAO (Friedhoff, Miller, and Karparkin 1978; Murphy et al. 1978). Thus, it is probable that many variables can influence platelet MAO activity as measured by the older methodologies using saline-washed platelets and platelet-rich plasma. The more recent promising and practical techniques for platelet isolation involving density gradient centrifugation with arabinogalactan, which can largely avoid sampling errors due to platelet heterogeneity (Friedhoff, Miller, and Karparkin 1978; Murphy et al. 1978), may resolve many of the current inconsistencies.

Reduced Platelet MAO Activity in Schizophrenic Patients

There is somewhat conflicting evidence that schizophrenic patients as a group, or particular subgroups of schizophrenics, have a decrease in mean platelet MAO activity; almost

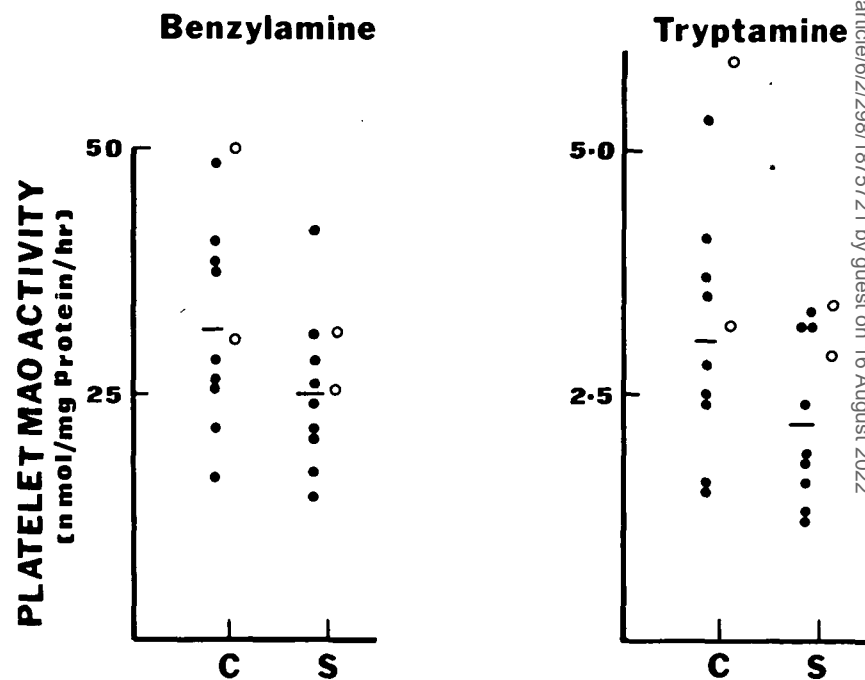
all studies have been conducted using the older platelet-rich-plasma or saline-washed-platelet methods. This evidence is reviewed in considerable detail by Murphy and Kalin (1980; this issue).

Because many variables including time, temperature, agitation, and speeds of centrifugation may influence platelet recovery from an individual patient, we controlled for these variables in a study of 11 schizophrenic patients and matched normal control subjects. Each patient and his control were sampled at the identical time, the specimens collected in a nonwettable, nonvacuum system, and the paired blood specimens were processed simultaneously

throughout platelet isolation and assay (Robinson et al. 1968). As shown in figure 3, the schizophrenic patients had a significantly lower mean platelet MAO activity than the matched group of age- and sex-matched normals. The difference in mean activity was significant with both benzylamine and tryptamine substrates. For every patient-control pair except one, the patient's MAO activity was lower than his matched control. This represents a replication of our previous findings with another series of carefully selected schizophrenic patients (Nies et al. 1974).

The fact that mean platelet MAO activity appears to be decreased in

Figure 3. Platelet MAO activities in 11 schizophrenic patients (S) and 11 normal controls (C)



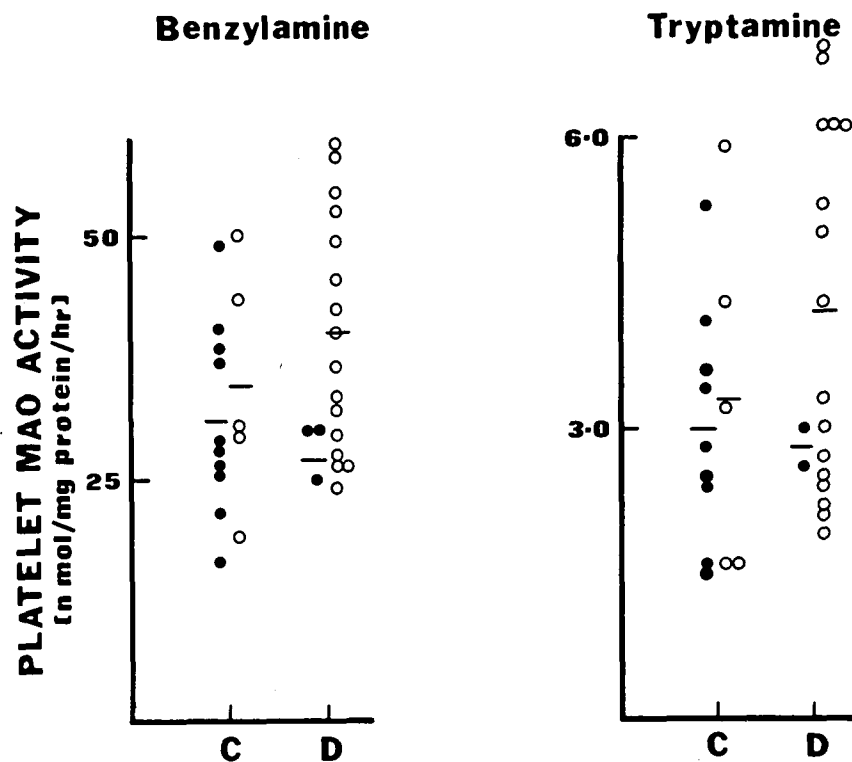
Activities (means and standard errors) with benzylamine and tryptamine substrates are shown for nine men (closed circles) and two women (open circles) in each group. Each matched pair had blood sampled, processed, and assayed simultaneously. Mean platelet MAO activity was significantly lower in schizophrenics for both substrates ($p < .05$, paired t test, two-tailed).

some chronic schizophrenic patients does not necessarily establish that this difference represents a genetic trait. As discussed above, several uncontrolled variables present in most such studies could account for reported differences, including concurrent or prior neuroleptic medication (Takahashi, Yamane, and Tani 1975; Friedhoff, Miller, and Weisenfreund 1978). Such drugs could have a long-lasting effect on some aspect of megakaryocyte and thrombocyte kinetics or enzyme protein synthesis within marrow elements (Pisciotta et al. 1965). Similarly, neuroleptics might indirectly influence platelet MAO through an effect on endogenous compounds, hormones, etc. (Ayitey-Smith and Kalsner 1977; Ho-Van-Hap, Babineau, and Berlinquet 1967). Considerable work needs to be done on this aspect of the relationship of platelet age, density, and enzyme activity to establish the significance of the reported finding of low platelet MAO activity in schizophrenic subgroups.

In a parallel study in which a series of depressed outpatients (all non-bipolar) were compared with an unmatched control group, platelet MAO activities tend to be higher in the depressed patients (figure 4). This could be attributed to the fact that the patient group is composed primarily of women, although it is not due to an age effect since mean ages did not differ. None of the depressed patients had received neuroleptics within at least 1 year of this study.

The higher platelet MAO activity in this series of depressed patients is consistent with our previous report of elevations of enzyme activity in a large series of patients with nonbipolar depressions (Nies et al. 1974). Although the reported lower platelet MAO in bipolar groups has received

Figure 4. Platelet MAO activities in 19 depressed outpatients (D) and 15 normal subjects (C)



Activities (means and standard errors) with benzylamine and tryptamine substrates are shown for men (closed circles) and women (open circles). Statistical tests for differences in means were not performed due to lack of controlled design of experiment.

wider attention (Murphy, Belmaker, and Wyatt 1974), it is interesting that several investigators have shown a consistent pattern of elevated platelet MAO activity in the larger population of nonbipolar depressions, as recently summarized by Mann (1979). High platelet MAO is associated with the severity of endogenous symptoms in recurrent unipolar patients (Mann 1979; Nies et al. 1975). These findings in depression, now replicated in a number of studies, do not seem to have received as much attention (although they should be of as much interest) as the platelet MAO-schizophrenia association.

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