MITOCHONDRIAL MONOAMINE OXIDASE

Studies on its activity in some psychiatric diseases

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ABSTRACT


Monoamine oxidase (E.C.1.4.3.4) (MAO) oxidatively deaminates the biogenic amines normally present in the organism. The activities of the neurons utilizing these amines i.e. noradrenaline, dopamine and serotonin, are supposed to be involved in the pathogenesis of various psychiatric diseases. It is speculated that the MAO activity is changed as well as the monoaminergic activity in some psychiatric disorders.

In the present thesis the MAO activity has been studied in brain tissue and in platelets in some psychiatric disorders. The result was as follows:

MAO activities in different parts of the human brain seem to be highly intercorrelated in each individual. The brain MAO activity is also weakly correlated both to the concentration of 5-HT and of 5-HIAA, which may indicate that the MAO activity reflects the serotoninergic turnover in the brain.

The MAO activity in brains from 15 suicides was compared to a control material of 20 individuals without known mental disorders, and it was found to be lower in the suicides in all 13 analysed brain parts. As eight of the patients had been chronic alcoholics, they were excluded and the remaining seven non-alcoholic suicides were tested as regards MAO activity by analysis of variance and still found to have significantly lower MAO activity than the controls.

The eight chronic alcoholics in the suicide series had the most significantly (p<0.005) reduction of the MAO activity as compared to the control group.

Rats were given chronic treatments with ethanol, either by 10 % ethanol as the only water supply or by exposition to ethanol vapor twice a day. In neither of these cases was the brain MAO activity changed as compared to control rats. The result supports the hypothesis that the low MAO activity found in alcoholic suicides most likely is related to a constitutional factor and not to a direct effect of the ethanol intake.

Platelet MAO activity was found to be significantly reduced in human alcoholics as compared to matched controls.

If samples were drawn from the alcoholic patients during their abstinence phase, there could be seen a transitory rise in the platelet MAO activity. This increased activity had its maximum after two weeks, and after four weeks the MAO activity had returned to the initial, low level.

No difference as regards MAO activity, neither in brain tissue nor in platelets, could be registered when chronic schizophrenics were compared to matched controls.

Reduced brain MAO activity was found in a group of patients diagnosed as cycloid psychoses when comparing the activity to controls or to the schizophrenic patients.

The platelet MAO activity was also found to be lower in cycloid psychoses than in a group of unipolar affective psychoses, who repeatedly have been found not to differ from normals.

These findings suggest that low MAO activities in brain and platelets reflect a phychic constitution in the individual making him more vulnerable for suicidal behaviour, ethanol abuse or cycloid psychosis.

Keywords: Monoamine oxidase, psychiatric disease, suicides, alcohol abuse, schizophrenica, cycloid psychoses.
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by

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Umeå 1978
The present thesis is mainly based on the following papers.


V  A. Wiberg: Increase in platelet monoamine oxidase activity during the abstinence after ethanol abuse. Manuscript.


In the following text the papers will be referred to by their Roman numerals; other references are indicated by Arabic numerals.
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INTRODUCTION

Monoamine oxidase (E.C.1.4.3.4.) (MAO) is one of the principal catalysts of the biological inactivation of monoamines normally present in the organism (1), with norepinephrine, dopamine and serotonin as the best studied and most widely distributed substrates (2). A general formula for the oxidative deamination of MAO can be expressed as follows:

\[
R-CH_2-NH_2 + O_2 + H_2O \rightarrow R-CHO + H_2O_2 + NH_3
\]

In the central nervous system the monoamines used as transmitter substances are deaminated by MAO, either after their release, after their re-uptake into the nerve endings or after leakage from intraneuronal storage vesicles (3). Another probable physiological function of MAO is to deaminate ingested exogenous amines. This is supported by the relatively high activities of the enzyme in the liver and the intestine (3).

In some psychiatric diseases it is speculated that there is a changed activity in the central nervous pathways which utilize some of the above-mentioned substances for transmission of the impulse. One of the reasons for this assumption is that drugs with a specific efficacy in these diseases, with few exceptions, act by changing the monoaminergic activity (4).

If the monoaminergic activity is changed and the MAO activity is changed as well, either primarily or secondarily, as a consequence of the changed monoaminergic turnover, it should be of great interest to study the enzyme activity. The reasons for this are that if the change is primary, it could be possible to get some insight in the molecular events involved in the pathogenesis of the disease. If the change in MAO activity should be secondary, the stability of the enzyme in post-mortem studies (5) could possibly give better information about monoaminergic turnover than direct estimation of the amines or of their metabolites.
Different forms of MAO

It has been shown that monoamine oxidase after treatment with detergent and extensive sonication can be separated in up to five discrete bands of activity by polyacrylamide gel electrophoresis (6). This result suggested the existence of multiple forms of the enzyme. At least one of these bands, however, was an artefact and furthermore it has not been possible to draw any definite conclusions about the nature of the enzyme forms found in the other bands, either as regards substrate specificity or sensitivity towards different inhibitors.

When Johnston in 1968 (7) introduced the irreversible MAO inhibitor clorgyline, it was shown to inhibit the MAO activity towards serotonin (5-HT) at much lower concentrations than were required to inhibit the activity towards benzylamine. He then classified the enzyme into two different forms on account of its preferential sensitivity to the inhibitor. The form which was inhibited by clorgyline was termed the A-form and the insensitive form was termed the B-form. Another inhibitor, deprenyl, (8) was shown to be more potent in inhibiting the so-called B-form. In the brain, serotonin seems to be a specific substrate for the A-form, while 3-phenylethylamine and benzylamine (9) as well as dopamine (10) are preferred substrates for the B-form. Tyramine (9) and tryptamine (11), on the other hand seem to be oxidized by both forms of the enzyme.

An intriguing question is whether the multiple forms of MAO represent different enzyme proteins (12) or if the different properties can be explained by differential behaviour of one enzyme in different environments (13), or even by a number of binding sites with different properties within one single active site (14).

The localization of MAO

MAO has been found in all vertebrates investigated and also in some invertebrates (1). It is present in most mammalian tissues
with a high activity in the liver, kidney and intestine and low or no activity at all in skeletal muscle and erythrocytes (15). In brain the enzyme is present both in the intra-neuronal as well as in the extra-neuronal tissue (16). It is firmly bound to the outer membrane of the mitochondria (17), which has made it very difficult to solubilize and purify (18, 19). It has been known that monoamine oxidase from liver and kidney mitochondria contains a covalently bound prosthetic group, FAD (20, 21), linked with a cysteineyl bond to the apoprotein (22). In respect to brain MAO, the question is still open whether the flavin is bound covalently or non-covalently to the MAO protein (23).

It is not yet clear if a metal ion is required for the function of monoamine oxidase (24). So far only iron has been found to be present in significant amounts in purified enzyme preparations (20). Studies with iron deficiency indicate that iron may play a role in the enzymatic activity, at least in the liver, heart and platelets. Whether iron functions as a cofactor or as a part of the enzyme protein or is needed for the synthesis of the protein is not yet clear (24).

The enzyme in the blood platelets seems to be essentially similar to that in other organs, and it is proposed that blood platelets can serve as a model for the CNS-amine-storing presynaptic nerve terminals (25). Although the brain MAO and platelet MAO have many properties in common, it may be noted that the platelet enzyme seems to exist exclusively in the B-form (26). There are, however, reports on the existence of two "B"-active sites in the platelet enzyme (27), but in a more recent investigation no support for more than one active site was found (28).

Brain MAO

A. General (II, VII)
The MAO activity in brain tissue does not seem to be uniformly distributed. The highest activities have been observed in
the hypothalamus and somewhat lower activities in the nucleus caudatus, the putamen, globus pallidus and the mesencephalon. The lowest activities have been found in the cortex regions (see II). This result is in agreement with several other investigations (5, 9, 29).

As for the multiple forms of the enzyme, two forms have been identified in the human brain (30). The ratio of the A-form to the B-form appears to be rather uniform in various areas, but neurons that contain specific amines may contain specific MAO enzymes and this may not be evident in larger sections of the brain that contain heterogenous populations of cells. In paper no II can be seen, however, that the ratio of β-phenylethylamine oxidizing activity to the tryptamine oxidizing activity is higher in e.g. the nucleus caudatus (1.55) than in the hippocampus (0.93).

The number of studies on MAO activity in brain tissue post-mortem are limited, probably due to difficulties inherent in studying autopsy specimens. Thus there are a lot of sources of error that might have an influence on the MAO activity. The cause of death, age, sex, medication and the time elapsed between death and autopsy are some variables that have to be taken into consideration. The stability of the brain enzyme, however, is rather good. The post-mortem changes were found to be almost negligible up to 4 hours at 33° or up to 120 hours at 5° (31) or by storage in airtight packages at -70° for several months (for a rev. see 5).

In a control material the patients must not have suffered from any kind of psychiatric or neurologic disease, as these might be involved in changes of the monoaminergic activity (see under "Previous studies on brain and platelet MAO in various psychiatric diseases"). As regards drugs, tricyclic antidepressives, with the exception of MAO inhibitors, are the only psychoactive drugs that have been reported to have any considerable ability to inhibit the enzyme (32). In in vitro experiments, some tricyclic agents have been found to inhibit preferentially the B-
form of the enzyme (33). In vivo, however, this effect has been
difficult to reproduce, possibly because the inhibition is re­
versible (34, 35, 36).

Robinson et al. (37) have found that the MAO activity increases
with increasing age using benzylamine as substrate. We have
found (see II) a positive correlation between age and β-phenyl­
ethylamine oxidizing activity, but no correlation between age
and MAO activity when tryptamine was used as substrate.

There are indications that there is a correlation between the
monoaminergic turnover and the MAO activity in brain. Thus in
three different parts of the human brain (VII) correlations, of
which three out of nine were on a significant level, were found
between the concentration of 5-HT and MAO activity. Twenty
human brains were investigated and the material included
patients that had died by heart infarction or malignant disease.
None of them had had neurological or psychiatrical diseases.
Correlations were also found between concentrations of 5-HIAA
and MAO activity (VII). In the five parts of the brains in­
vestigated 16 out of 25 possible analyses were positive, and in
three cases on a significant level. This seems to be an indica­
tion for a correlation between serotonergic activity in the
brain and MAO activity. Whether such a correlation also exists
with other monoamine transmitters than serotonin has to be in­
vestigated.

B. Regulation (VII)
Analyses made on different mouse strains indicate that the MAO
activity in brain is dependent on the genotype (38). In man we
have found a high intercorrelation of the MAO activity between
different parts of the brain (VII). This could be interpreted
as a dependence of the MAO activity on genetic factors.

Experimentally, changes in the MAO activity in brain are hard
to induce. However, some alteration of the MAO activity might
be caused by steroid-hormones (39, 40). Thus, e.g. progesterone
has been found to increase the MAO activity, and oestrogen to
to lower the MAO activity in the uterus, ovaries and adrenal glands and also to some extent in the hypothalamus of the rat. Stress (41) as well as repeated treatment with electroconvulsive shocks (42) have been shown to increase the brain MAO in rat. Recently it has also been shown that large doses of alcohol given in acute experiments raises the activity (43).

Platelet MAO

A. General (I)
The platelet MAO seems to increase with age in a similar manner to the brain MAO (37). Women have been found to have on an average, 10% higher MAO activity than men (37). Some authors have found a bimodal distribution (44) and others have found an unimodal distribution (45) of the MAO activity in normals. The interindividual difference of platelet MAO activity is about 10 fold (46).

The enzyme stored as platelet rich plasma in -70° seems to be very stable. Blood samples that have been kept in the deep-freeze on up to 18 months have been examined for platelet MAO on different occasions. The MAO activity showed to be non-correlated to the storage-time.

Neither have others (47) noted any change in the MAO activity when samples have been kept in -70°.
In paper no I the molecular turnover numbers for some substrates, and average number of monoamine oxidase molecules per mitochondrion and the area of the platelet mitochondrial membrane occupied by monoamine oxidases have been calculated.

The platelet preparation was titrated with a known amount of the MAO inhibitor pargyline. Pargyline inhibits monoamine oxidase irreversibly in a ratio of 1:1, i.e. the amount of enzyme inhibited is equal to the amount of pargyline added (48). Further calculations using Avogadro's number and platelet counts gave the result that each platelet contained 900 molecules of monoamine oxidase. An average number of 3.5 mitochondria per thrombocyte (Solatunturi, personal communication) gives the result of 200-300 molecules of the enzyme in each thrombocyte mitochondrion. Calculations of the total area of the outer membrane of each mitochondrion that is occupied by molecules of monoamine oxidase, presuming that the enzyme is a spherical protein with a density of 1.4 and a molecular weight of about 100 000 - as has been shown to be the case for the enzyme from other organs (3, 20, 49), indicated that the enzyme should occupy 1/5000 of a mitochondrion with the dimension 10 x 1 μm.

The molecular turnover numbers obtained in this study, 720 and 1470 for tyramine and benzylamine, respectively, are somewhat higher than was found in the human brain tissue, 340 respectively 280. Molecular turnover numbers from other organs, mainly from animals, (50, 51) seem to be comparable with those of the brain. Thus there might well be a somewhat higher catalytic activity for platelet MAO than for MAO in other organs.

B. Regulation

There are strong evidences, that the platelet MAO activity is controlled by genetic factors. This is, for instance, demonstrated in a study in which the platelet MAO activity was found to be highly correlated between monozygotic twins when compared to the correlation between other sib pairs (52, 53). That platelet MAO activity is highly replicable, has been proved by analysing samples taken from the same individuals one week to one year
apart. These samples showed a very small variance (54). This suggests that platelet MAO represents a relatively stable characteristic of the individual.

There are some psychoactive drugs that are known to inhibit the platelet MAO activity, e.g. irreversible MAO-inhibitors (55), while neuroleptics do not (47). The tricyclic antidepressant drugs inhibit the enzyme reversible, but high concentrations are required (55). Lithium treatment in affective disorders seems to influence the MAO activity. In a preliminary study (56) the patients who had received Lithium Carbonate had reduced MAO activity as compared to untreated patients. This is in accordance with a previous finding by Pandey et al. (57) but in contrast to Bockar et al. (58). Another factor which may affect the platelet MAO activity is the presence of steroid hormones, especially progesterone and oestrogen. The MAO activity seems to fluctuate with the menstrual cycle and there are reports of up to a 20% increase in MAO activity during the preovulatory period (59). Non-specific stress induced by adrenaline given subcutaneously caused an increase in MAO activity, but the protein content (60) as well as the platelet count (61) was increased simultaneously.

The activity of the platelet MAO has been reported to be related to the psychological behaviour and the personality in normals. Murphy et al. (62) observed that individuals with low platelet MAO were more orientated towards experience seeking, disinhibition or boredom. In a prospective study (63) criminality, suicide or attempted suicide or psychiatric disorders were shown to be more common among subjects with low MAO activity.

BRAIN AND PLATELET MAO UNDER DIFFERENT PSYCHIATRIC CONDITIONS

Previous studies on brain and platelet MAO in various psychiatric diseases

There are few previous studies on brain tissue MAO activity in psychiatric diseases. The MAO activity in brains from schizo-
phrenics appears to be normal according to some authors (31, 64, 65, 66, 67). For depressive suicides and alcoholic suicides Grote (29) could not detect any changed MAO activity.

Alterations in platelet MAO activity in affective disorders have been described in many studies. Murphy and Weiss (68) have reported that the MAO activity is decreased in bipolar depressed patients as compared to unipolar depressed patients and this study was confirmed by others (e.g. 69). In contrast Belmaker et al. (70) and Nies et al. (52) found an increased MAO activity in bipolar depressives. The platelet MAO activity in unipolar depressive patients has repeatedly been found to be normal (68, 71).

In a number of studies the platelet MAO has been estimated in chronic schizophrenia and in different subgroups of schizophrenia (for reviews see 47, 54) but the results appear to be contradictory.

<table>
<thead>
<tr>
<th>Author (ref. no)</th>
<th>Patient subtypes</th>
<th>Percentage of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy &amp; Wyatt, 1972 (76)</td>
<td>Chronic and acute</td>
<td>41</td>
</tr>
<tr>
<td>Wyatt et al., 1973 (53)</td>
<td>Chronic and acute</td>
<td>61</td>
</tr>
<tr>
<td>Shaskan &amp; Becker, 1974 (72)</td>
<td>Anergic outpatients</td>
<td>No difference</td>
</tr>
<tr>
<td>Friedman et al., 1974 (73)</td>
<td>Remitting</td>
<td>83 (NS)</td>
</tr>
<tr>
<td>Nies et al., 1974 (52)</td>
<td>Less than 1 year of hospitalization</td>
<td>72-86&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Meltzer &amp; Stahl, 1974 (74)</td>
<td>Chronic</td>
<td>32-52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carpenter et al., 1975 (77)</td>
<td>Acute</td>
<td>97 (NS)</td>
</tr>
<tr>
<td>Zeller et al., 1975 (78)</td>
<td>Acute and chronic</td>
<td>39-43&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Domino &amp; Khanna, 1976 (75)</td>
<td>Chronic</td>
<td>46</td>
</tr>
<tr>
<td>White et al., 1976 (79)</td>
<td>Chronic</td>
<td>90 (NS)</td>
</tr>
<tr>
<td>Wyatt &amp; Murphy, 1976 (47)</td>
<td>Chronic</td>
<td>71</td>
</tr>
<tr>
<td>Berger et al., 1978 (80)</td>
<td>Chronic</td>
<td>71</td>
</tr>
</tbody>
</table>

NS not significant
<sup>a</sup> used multiple substrates
As shown in the table above some authors have found a decreased activity, others could not find any changed activity compared to normals and, further, others have found changes in substrate specificity (52, 74) and enzyme kinetic aberrations (81, 82).

Sandler et al. (83) have suggested that there is a defect in platelet MAO activity in patients with migraine. In other psychiatric disorders in which changes in activities in the monoaminergic systems have been registered e.g. Down's syndrome, reduced platelet MAO activity has been found (84), while in infantile autism, no change in MAO activity has been found (85).

**Suicides**

A. Brain (II)

According to the current monoamine hypothesis the monoaminergic activity is low in depressive states. To test if the MAO activity is altered in such states, the enzyme activity has been analysed in the brains from suicides (II). It was presumed that at least some of the patients with suicidal behaviour would have a different, probably lower monoaminergic activity than normals. Thirteen parts of the brain in 15 patients who had committed suicide have been dissected out. As controls, matched for age and sex 20 persons were selected who had died from accidents and who had never suffered from neurologic or psychiatric disease. When comparing the MAO activity between the control series and the suicide series there was found a lower activity in the suicides in all parts of the brain, and this was true, regardless of the substrate used, tryptamine or β-phenylethylamine. The age of the patient and the time variables e.g. time kept at room temperature, time between death and autopsy were also analysed and did not appear to have any influence on the results obtained. Of these 15 patients, however, eight has also been alcoholics. If they were excluded, the result was as follows: The non-alcoholic suicides had significantly (p < 0.01) lower MAO activity than the controls, when the difference between the brains as a whole were tested by analysis of variance. (This is not included in paper II).
This difference in MAO activity between controls and suicides is not in agreement with Grote et al. (29). Different methods and different substrates when estimating the MAO activity and the choice of control material might be account for the different results. The finding that all of the suicides had lowered brain MAO activities is somewhat surprising since only a minor number of suicides usually have suffered from affective disorders (see 86). It thus seems as if suicidal behaviour rather than affective disorder may be the crucial syndrome linked to low MAO activity.

B. Platelets
Suicide or attempted suicide has been found to be more frequent among individuals with low platelet MAO (63). Buchsbaum et al. (86) have further found that suicide and attempted suicide are associated with low platelet MAO activity and augmenting response in visual average evoked response (VAER). Recently Gottfries et al. (56) have investigated a large group of patients with affective disorders. Among those patients some had committed suicide by means of violent methods and those patients were found to have significantly lower platelet MAO activity than the other patients.

Alcohol abuse

A. Human brain (II)
Studying the data from the suicide series (II) it was obvious that eight out of the 15 suicides (before death) had heavily abused alcohol and could be considered chronic alcoholics. Thus rearrangement of the suicide group in an alcoholic suicide group (n = 8) and a non-alcoholic suicide group (n = 7) gave the result that the most significant (p < 0.005) reduction of the MAO activity occurred in the alcoholic suicide group. Also compared to the suicide group without ethanol abuse significantly (p < 0.05) lower activity were found, at least when tryptamine was used as substrate. A lowered brain MAO activity thus seems to be related not only to suicidal behaviour but also to alcohol abuse.
B. Rat brain (III)
To investigate if the decreased MAO activity found in alcoholic suicides in man, could be due to a direct effect of the ethanol, male Sprague-Dawley rats were forced to accept alcohol intake in two ways (III). One group of rats was given 10% ethanol as the only water supply for 34 weeks. The average weekly consumption of ethanol increased during the treatment from 2.1 g/kg/day to 5.8 g/kg/day and a blood ethanol level of about 2 o/oo was recorded. In the second group the rats were exposed to ethanol vapour 5 hrs a day for 7 weeks. With this treatment the rats reached blood ethanol levels of 4-5 o/oo.

The MAO activity of the whole rat brain was estimated both in a synaptosomal fraction and also in an extra-synaptosomal mitochondrial fraction. Three different methods, an oxygen-polarographic, a spectrophotometric and a radioactive method, and five different substrates with different specificity towards the two forms of the enzyme were used. But regardless of method or substrate there could not be found any change in the MAO activity as a result of the ethanol intake when compared to control rats. Of course these rat experiments are not conclusive as regards the situation with human alcoholics but it seems that this result makes it less likely that the lowered MAO activity found in the human alcoholics was due to an effect of ethanol. This has caused us to put forward the hypothesis that a predisposition to certain psychiatric diseases e.g. ethanol abuse is due to constitutional factors and that this is also reflected in a low monoamine oxidase activity.

C. Platelets (IV, V)
The platelet MAO activity of 24 human alcoholic patients admitted to a psychiatric hospital has been studied (IV). The patients were all heavily addicted to alcohol and showed an active withdrawal syndrome after cessation of alcohol intake. Blood samples were drawn as soon as possible after admission, as well as later in the abstinence phase. As controls, staff at the hospital were chosen. They were matched for age and sex and didn't suffer from any kind of drug or alcohol misuse. The alcoholics in the present
study didn't reach such low concentrations in serum iron, transferrin or accumulation of acetaldehyde that has been shown to lower the MAO activity (24, 87).

Platelet MAO activity in samples taken on day No 0-3 in the abstinence phase was significantly reduced as compared to the controls. This was true for both substrates used (β-phenylethylamine, tryptamine). The same result has later been found by others (88, 89).

As regards the platelet number, thrombocytopenia has been seen in chronic alcoholics with delirium tremens (90), but the platelet count rapidly have returned in the abstinence and a thrombocytosis has occurred. However, since we express the MAO activity in relation to the platelet count, these findings do not bear any obvious relationship to the results described above.

If the alcoholic patients were followed during their abstinence phase a transitory rise in MAO activity was observed during that period (V). This increased activity had its maximum after two weeks, and after four weeks the MAO activity had returned to the initial, low level. One possible explanation to this peak in MAO activity may be a result of a transitory increase in the turnover of noradrenaline that has been reported to occur in the abstinence phase (91). These observations can be an indication that the abstinence phase might be longer than is usually anticipated. The result from another study on chronic alcoholics is partly in contrast to ours (V) and to that of v. Knorring and Oreland (89), since the decreased platelet MAO activity found was interpreted as an acute inhibition of the enzyme activity which returned to normal values after a certain time of ethanol withdrawal (92).

Schizophrenics

A. Brain (VI)

There are two major hypotheses dominating investigations into the biological substrate of schizophrenia: one suggesting that
schizophrenia reflects a functional overactivity in dopaminergic systems, the other that a production of an endogenous psychotogen is responsible for the symptoms of schizophrenia. To test these hypotheses, various assays of the relative activity of enzymes involved in the metabolism of the biogenic amines have been performed.

Concerning the MAO activity in the brains of schizophrenics there are a few studies but no differences from controls have been found (31, 65, 67). In studies as these it is, however, very difficult to compare the patient materials to one another. In the present study 12 cases who fulfilled the criteria of Bleuler for the diagnosis of schizophrenia (93) have been analysed for brain MAO activity (VI). As controls matched for sex and age 15 cases without known neurological or psychiatric disease were selected. The result is in agreement with previous reports, i.e. no difference in MAO activity between chronic schizophrenics and controls.

B. Platelets (VI)
Many studies have been performed on platelet MAO activity in patients with schizophrenia (see table 1). However, the results obtained are contradictory. The main reasons for this might possibly be the different criteria used for the diagnosis of schizophrenia and the selection of control materials. The MAO activity also seems to scatter widely in both chronic schizophrenic patients and normals. Some controls even have MAO activities below the mean for schizophrenics. Only one study has reported of no overlaps between patients and controls (75).

We selected 14 patients who were diagnosed as chronic schizophrenics according to the criteria of Bleuler and 11 patients with the same diagnosis but also with alcohol in their anamnesis to form another group (VI). To match the two groups of schizophrenics one group of controls was formed from healthy volunteers. Another group of controls was formed from 14 patients with chronic diseases such as epileptic defect states and personality disorders, who were hospitalized under the same condi-
tions as the schizophrenics. Comparison of the platelet MAO activities in the schizophrenics with the control groups gave no sign of any difference between them. Nor did the alcoholic schizophrenics differ from healthy volunteers as regards MAO activity. From this result we can draw the conclusion that ethanol abuse cannot explain the finding of low platelet MAO activity that has been reported elsewhere in schizophrenics. It also indicates that the cause of ethanol abuse among schizophrenics may be other than the vulnerable personality that is supposed to cause the abuse in otherwise healthy individuals.

Cycloid psychosis

A. Brain (VI)
Four patients with mood swings and diagnosed as cycloid psychotics were studied in the same investigation as the schizophrenics (VI). In all 13 parts of the brain the MAO activity was found to be lower in the group of cycloid psychotics as compared to controls or to the group diagnosed as schizophrenics. Statistically significantly lower activities were found in the thalamus, hippocampus, cortex gyrus hippocampus, cortex gyrus cinguli and cortex frontalis.

B. Platelets (VI)
In the present study (VI) we have divided a group of patients with affective disorders into cycloid psychoses and unipolar affective psychoses. The platelet MAO activity in the group of cycloid psychoses was significantly lower than in a group of unipolar affective psychoses. Since the latter group, however, repeatedly has been found not to differ from normals we conclude that cycloid psychotics have lowered platelet MAO activity (68, 71).

INTERPRETATION

As for the interpretation of the results, it has to be considered if there is a correlation between the platelet MAO activity and the brain MAO activity. So far no direct studies provide
conclusive evidence of such a relationship. Evidence is, however, accumulating which tends to support a correlation between the two MAO activities. Thus, we have found low MAO activities both in brain and platelets in patients with suicidal behaviour (II, 56) alcoholics (II, IV) and in cycloid psychotics (VI), while, on the other hand, the two activities were found to be normal in schizophrenics (VI). Such a correlation would be of great value in that blood samples for estimation of platelet MAO activity are easily obtained and hence conveniently provide information about the MAO activity in the brain.

Brain MAO activity may, in accordance with the present results (VII), give an indication of the serotonergic activity in the brain. Changes in the serotonergic activity are, in turn, considered to be of importance for the pathogenesis of some psychiatric diseases. So far, however, this seems to have been directly confirmed only for suicides using violent methods, in whom lowered concentrations of 5-HIAA in the cerebrospinal fluid have been found by Åsberg et al. (94). It is thus notable that suicidal behaviour is one of the psychiatric disorders in which low platelet as well as low brain MAO activities have been registered (56, II). The findings of normal concentrations of 5-HIAA in brain tissue from suicides (95), are not, however, easily linked together with the assumption outlined above. Although there are earlier studies in which lowered 5-HIAA levels have been found in brains from suicides (96, 97), the technical difficulties seem to have been best handled in the study of Gottfries et al. (95).

Since both platelet and brain MAO activities seem to be rather stable characteristics for each individual, with, at least partly, a genetic regulation, it would be reasonable to assume that low MAO activities in brain and platelets reflect a psychic constitution in the individual making him more vulnerable for the disorders found to be correlated to low MAO activity (see fig. below). A similar hypothesis was originally presented by Murphy and collaborators (see 98) as regards low platelet MAO and vulnerability to schizophrenia. Although the hypothesis does not
seem to be valid for this disease, according to the present results (VI), support for its validity in connection to other disorders, apart from those included in the present study, has recently been presented in a prospective study, where a significantly higher incidence of suicide attempts, psychosocial problems or criminality have been found in low platelet MAO probands (63). Further support was also added in another recent study of Murphy et al. (62), who found the platelet MAO activity to be lower in normals with disinhibition and who feel boredom or who are experience seekers.

In the figure shown below our current proposal of the logical connection between the present results are visualized. It may unnecessary to add that a lot of questions remain to be answered in such a vast complex of interrelated psychiatrically and biochemically intricate problems as this.

![Diagram showing low MAO in CNS and platelets leading to constitutionally low monoaminergic (serotonergic?) activity, resulting in cycloid psychosis, suicidal behaviour, and disposition for (ethanol) abuse.](image-url)
GENERAL SUMMARY

1. The number of monoamine oxidase molecules in human blood platelets have been estimated to be about 900 per platelet and 200-300 per platelet mitochondrion. Further calculations indicated that 1/5000 of a platelet mitochondrial membrane is occupied by monoamine oxidases.

The molecular turnover numbers obtained in platelets for tyramine and benzylamine were 720 and 1470 respectively, which are somewhat higher than those found in human brain tissue, 340 and 280 respectively. (I).

2. MAO activities in different parts of the human brain seem to be highly intercorrelated in each individual. The brain MAO activity is also weakly correlated both to the concentration of 5-HT and of 5-HIAA, which may indicate that the MAO activity reflects the serotonergic turnover in the brain. (VII).

3. The MAO activity in brains from 15 suicides was compared to a control material of 20 individuals without known mental disorder, and it was found to be lower in the suicides in all 13 analysed brain parts. As eight of the patients had been chronic alcoholics, they were excluded and the remaining seven non-alcoholic suicides were tested as regards MAO activity by analysis of variance and still found to have significantly lower MAO activity than the controls. (II).

4. The eight chronic alcoholics in the suicide series had the most significantly (p < 0.005) reduction of the MAO activity as compared to the control group. (II).

5. Rats were given chronic treatments with ethanol, either by 10 % ethanol as the only water supply or by exposition to ethanol vapor twice a day. In neither of the cases was the brain MAO activity changed as compared to control rats. The result supports the hypothesis that the low MAO activity found in alcoholic suicides most likely is related to a con-
stitutional factor and not to a direct effect of the ethanol intake. (III).

6. Platelet MAO activity was found to be significantly reduced in human alcoholics as compared to matched controls. (IV).

7. If samples were drawn from the alcoholic patients during their abstinence phase, there could be seen a transitory rise in the platelet MAO activity. This increased activity had its maximum after two weeks, and after four weeks the MAO activity had returned to the initial, low level. (IV, V).

8. No difference as regards MAO activity, neither in brain tissue nor in platelets, could be registered when chronic schizophrenics were compared to matched controls. (VI).

9. Reduced brain MAO activity was found in a group of patients diagnosed as cycloid psychoses when comparing the activity to controls or to the schizophrenic patients.

The platelet MAO activity was also found to be lower in cycloid psychoses than in a group of unipolar affective psychoses, who repeatedly have been found not to differ from normals. (VI).

These findings suggest that low MAO activities in brain and platelets reflect a psychic constitution in the individual making him more vulnerable for suicidal behaviour, ethanol abuse or cycloid psychosis.
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