Therapy-Resistant Depressions. 
Biochemical and Pharmacological Considerations

Contributions to biochemistry

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1. Basic data and problem definition

My argument will be structured as follows. I shall begin with two statements which will be formulated but not presented for discussion. On the basis of these statements I shall pose a question. My attempt to answer it will be the principal feature of my argument.

First statement: all known psychotropic drugs primarily exert an influence on impulse transmission in central synapses. The antidepressants are no exception to this rule. It is more specifically the monoaminergic synapse — the synapse in which a monoamine (MA) acts as transmitter — that is influenced by antidepressants.

Cerebral monoamines, i.e. noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT; serotonin), are stored largely in physiologically inactive form in vesicles localized at the axon end. This end is also the site of numerous mitochondria which contain monoamine oxidase (MAO), the enzyme which decomposes MA. Impulse transmission in a MA-ergic synapse conceivably takes place as follows (Akert and Waser 1969). When an impulse arrives at the axon end, some of the vesicles release their contents into the synaptic cleft (Fig. 1). The transmitter induces in the postsynaptic membrane a permeability change which is the core of a new impulse. After having transmitted the information the transmitter disappears, partly by diffusion to the bloodstream and by extraneuronal degradation but largely by active absorption from the synaptic cleft, via the cytoplasm, back to the vesicles. MAO prevents excessive accumulation of non-bound, i.e. physiologically active transmitter substance in the cytoplasm during its transport from and back to the vesicles.

![Diagram of monoaminergic synapse in the brain](diagram)

Fig. 1. Diagram of monoaminergic synapse in the brain  
MA = monoamine;  
MAO = monoamine oxidase
Antidepressants influence this system in the following manner (Schildkraut 1970). MAO inhibitors inactivate MAO and thus inhibit the intraneuronal degradation of MA. The result is a "leakage" of non-bound MA to the synaptic cleft. Tricyclic antidepressants block the "MA pump", i.e. the transport of MA from the synaptic cleft back to the synaptic vesicles. The two types of antidepressants now in use are unrelated as to chemical structure; moreover, they influence the central MA metabolism in different ways. Nevertheless they produce the same net effect: they increase the concentration of physiologically active MA in the synapse, thus probably increasing the activity of MA-ergic neuronal systems. There are indications that the therapeutic action of antidepressants is based on their MA-potentiating influence.

Second statement: antidepressants can have a mood-improving effect in depressions. However, this statement is subject to at least two restrictions. To begin with, these agents are not in all types of depression equally effective. The syndrome known as endogenous depression provides an obvious indication of choice. But even within the limits of a given syndrome (and this is the second restriction), not all patients show improvement. The improvement rate attained with antidepressants in endogenous depression is about 60-65% (Klerman and Cole 1965).

The same applies to other biological methods of treating depressions. In the syndrome of endogenous depression, ECT is still the therapy with the highest chance of success: a chance which approximates 90%. Results obtained in other types of depression are substantially less favourable (Hordern et al. 1965).

A very recent therapy is that based on sleep deprivation. The patient is systematically deprived of sleep throughout several nights per week. Investigations made in our department have revealed the same phenomenon: some depressive patients show a strikingly favourable response to this therapy, even if this is often only temporary, whereas other patients with similar symptoms show no response at all.

Questions. We have made two statements: antidepressants increase the amount of MA at the central receptors; antidepressants are effective in some, but quite ineffective in other patients, even if they belong to the same diagnostic category. Three questions result from these statements.

1. Does a central MA deficiency occur in depressive patients?
2. If so, is this disorder present in only a proportion of the patients?
3. If so, can this explain the apparent selectivity of antidepressants in the sense that particularly MA-deficient patients benefit from this type of therapy?

2. Central MA deficiency in depressive patients

The answer to the first question is affirmative. There are phenomena which indicate that disorders of the MA metabolism can occur in the brain in depressive patients. I shall list the most important of these phenomena, confining myself to findings which directly concern the CNS.

Postmortem studies. The 5-HT concentration found in the brain stem in suicide victims was lower than that found in a comparable control group. A decreased concentration of a given compound can indicate either decreased synthesis or increased degradation. Since not only the 5-HT concentration but also that of 5-hydroxyindoleacetic acid (5-HIAA: the principal 5-HT metabolite) proved to be diminished, decreased 5-HT
synthesis must have been involved in the abovementioned individuals. So far, three independent groups of investigators have carried out postmortem studies of suicide victims (Shaw et al. 1967; Bourne et al. 1968; Pare et al. 1969). Their results are not quite identical but point in the same direction. Unfortunately, it was impossible to obtain sufficient data on the histories of these suicide victims and on the nature of their depressions. Psychopathological heterogeneity of the groups perhaps explains why the results were not entirely in agreement.

**CSF studies.** A second source of information is the concentration of MA metabolites in the CSF.

Studies of this type are based on the following line of argument. The concentration of a MA metabolite in the CNS is related to the amount of the corresponding MA which is locally metabolized. Moreover, there is a relationship between the concentration of a MA metabolite in brain and spinal cord, and that in CSF. In any case this applies to CSF and adjacent parts of brain and spinal cord. According to this line of reasoning, the CSF concentration of a MA metabolite reflects the amount of the mother amine which is decomposed in the CNS.

The CSF concentration of 5-HIAA and that of the DA metabolite homovanillic acid (HVA) have both been found decreased in depressive patients by several (but not by all) investigators. Reviews have been published by Mendels et al. (1972) and by Papeschi and McClure (1971). A survey of the various results shows fair agreement of the values found in depressive patients, but substantial differences within the control groups. This may be due to the fact that none of the investigators has so far been able to use normal controls. Controls in these studies are invariably non-depressive hospital patients, often originating from heterogeneous populations.

Our next consideration is the NA metabolism in so far as it is reflected in the CSF. Whereas peripheral NA is largely decomposed to vanillylmandelic acid (VMA), the principal NA metabolite in the brain is 3-methoxy-4-hydroxyphenylglycol (MHPG). It was initially assumed that all MHPG excreted in the urine was of cerebral origin, and that consequently the renal MHPG should be a fairly exact index of central NA turnover. This has proved to be a fallacy. Recent studies in non-human primates suggest that about 50% of the urinary MHPG originates from the periphery (Maas et al. 1972a). The peripheral NA pool, however, is much larger than the cerebral. In other words: while MHPG is the principal central NA metabolite, it is only of subordinate importance as a peripheral NA metabolite. The conclusion that urinary MHPG gives information on the central NA metabolism, but not very exact information, thus remains valid.

Such little research as has so far been carried out, has not yielded unequivocal results. In depressions, normal as well as decreased MHPG concentrations have been found in the CSF (e.g. Wilk et al. 1972). In a well-designed study, Maas et al. (1972) found the renal MHPG excretion to be decreased in depressions. It is to be noted in this respect that MHPG is a compound which it is still difficult to determine reliably, so that all results must be regarded with reservations.

**Probenecid technique.** The introduction of the probenecid technique added a new dimension to the study of the central MA metabolism in living human individuals. Probenecid is a substance which inhibits the transport of acid MA metabolites from the CNS to the blood stream. Consequently these metabolites accumulate, and their rate of accumulation is a measure of the turnover of the corresponding mother amines.
Slight accumulation suggests a low production of these metabolites, therefore a low degree of degradation of the mother amines, and therefore a low turnover of the mother amines. Marked accumulation suggests the reverse: high production of metabolites, a high degree of degradation of the mother amines, and therefore a high turnover of the mother amines (Roos and Sjöström 1969; Van Praag 1969; Van Praag et al. 1970; Korf and Van Praag 1971; Tamarkin et al. 1970; Bowers 1972; Goodwin et al. 1973; Van Praag et al. 1973).

The response of the acid MA metabolites in the CSF to probenecid is not only dependent on the rate at which they are produced but also on other factors. An important factor is the amount of probenecid which reaches the CNS (Korf and Van Praag 1971). The more probenecid in the CSF, the more marked the accumulation. This applies to 5-HIAA as well as to HVA. It is therefore necessary in the probenecid test to administer the maximum amount tolerated by man. This amount was found to be 5 g in 5 hours. We have reasons, moreover, to assume that at this dosage the transport of acid MA metabolites from the CNS is blocked completely (Van Praag et al. 1973).

In our department the procedure of the probenecid test is as follows. A lumbar puncture is carried out on day 1. In the morning of day 3 the patient is given 5 g probenecid in 5 hours (of which 1 g is given by infusion). A second lumbar puncture is performed 8 hours after starting probenecid administration. The CSF concentrations of probenecid, 5-HIAA and HVA are determined (Korf et al. 1971; Korf and Van Praag 1971). The patient is confined to bed on the lumbar puncture days.

I mention the results obtained in this way in 38 depressive patients and 12 non-depressive controls (Van Praag et al. 1973). In the depressive group the 5-HIAA accumulation was significantly smaller than that in the control group. The same applies to the HVA accumulation, which in the depression group was decreased as compared with that in the controls (table 1). Probenecid concentrations varied within normal limits. We interpret these findings as suggesting that the turnover of 5 HT and DA in the brains is lower in depressive patients than in controls. These results therefore point in the same direction as the postmortem findings.

3. Explanation of the central MA deficiency

How to explain the apparently decreased central MA turnover in depressive patients? So far as the 5-HT metabolism is concerned, two observations may be of significance.

There are strong indications that the rate of cerebral 5-HT synthesis is largely determined by the amount of tryptophan which is locally available. The cerebral tryptophan concentration in its turn is closely related to the plasma concentration of free tryptophan, i.e. the tryptophan fraction not bound to serum albumins (Knott and Curzon 1972).

Table 1 Probenecid test results in depressive patients and controls

<table>
<thead>
<tr>
<th>Number of test subjects</th>
<th>CSF 5-HIAA (ng/ml)</th>
<th>CSF HVA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After probenecid</td>
</tr>
<tr>
<td>Controls</td>
<td>± 10.3</td>
<td>± 46.7</td>
</tr>
<tr>
<td>Depression</td>
<td>± 8.5</td>
<td>± 33.4</td>
</tr>
</tbody>
</table>
It was recently reported by *Coppen* et al. (1972, 1972a) that the serum concentration of free tryptophan and the CSF concentration of tryptophan were lower in depressive patients than in a matched control group (table 2). Should the CSF concentration of tryptophan be representative of the situation in the brain, then *Coppen*’s finding could explain the decreased 5-HT turnover suspected on the basis of the probenecid test.

| Table 2 CSF tryptophan, plasma total and free tryptophan in depression and controls (Coppen et al. 1972) |
|---------------------------------|-------------------------------|------------------|
| CSF tryptophan (ng/ml) | Plasma tryptophan (μg/ml) | Free |
| Controls | 488 ± 188 | 11.9 ± 0.49 | 1.34 ± 0.09 |
| Depression | 260 ± 106 | 12.5 ± 0.74 | 0.86 ± 0.06 |

There are also indications suggestive of a different explanation: a reduced capacity to convert tryptophan to 5-HT (*Van Praag* et al. 1973a). A series of depressive patients were submitted to an oral load of 5 g L-tryptophan, whereupon the CSF concentrations of tryptophan and 5-HIAA were determined. In different patients the lumbar puncture was performed at different intervals after tryptophan loading. *Eccleston* et al. (1970) did the same in a group of neurological patients without psychiatric symptoms. In the depressive patients the tryptophan concentration had tripled 1 hour after loading; at that time it hardly showed any change in the non-depressive patients. Eight hours after loading, moreover, the 5-HIAA concentration in the CSF showed a less marked increase in the depressive than in the non-depressive group. More tryptophan in the CSF, and less 5-HIAA seems to suggest that the tryptophan administered "congests" in the CNS in depressive patients, that it is less readily converted to 5-HT. This phenomenon, too, could explain a diminished 5-HT turnover.

4. Depressions with and without central MA deficiency

We must now consider the second basic question. If disorders in the central MA metabolism occur in depressions, are they encountered in all patients, or only in certain categories, or distributed at random over the various categories?

Let us once more consider the results of the aforementioned study with probenecid in 38 depressive patients (*Van Praag* et al. 1973). Of these patients, 28 showed the symptoms of endogenous depression and 10 showed those of neurotic depression. The entire depression group included 12 patients whose 5-HIAA response to probenecid was subnormal, that is to say outside the range in the control group. All these patients were in the endogenous group (Fig. 2). From this fact I am inclined to conclude that the group of endogenous depressions, although fairly homogeneous in psychopathological terms, is heterogeneous in biochemical terms.

Perhaps one may go one step further and assume that the syndrome of endogenous depression does not always involve the same cerebral substrate. It is a wellknown fact in internal medicine that congruence of symptomatology does not necessarily imply congruence as to pathogenesis; that, in other words, it is possible that within the same diagnostic category a given metabolic disorder can be present in one patient and absent in another. In this context the anaemia syndrome and the jaundice syndrome come to mind. Anaemic patients show considerable similarities in clinical symptoms, but the
pathogenesis of this syndrome can vary widely. The same applies to the jaundice syndrome. Without any justification, this possibility is always ignored in biological psychiatry.

The depression group included 14 patients with a subnormal HVA response to probenecid (Fig. 3); the depression had been diagnosed as endogenous in 11 and as neurotic in 3 of these patients. Nevertheless all these patients showed one common characteristic: motor retardation. A subnormal response of HVA to probenecid has also been observed in Parkinson's disease (Olsson and Roos 1968; Lakke et al. 1972). This syndrome also encompasses hypokinesia. It is therefore quite possible that a diminished cerebral DA turnover (which the subnormal HVA suggests) is not specific of a given disease entity (in this case Parkinson's disease), but rather characterizes a certain functional condition: in this case hypokinesia.

To summarize: it can be stated that these findings indicate that disorders in the central MA metabolism are not a universal phenomenon in depressions, nor one that is randomly distributed through the group, but rather one that seems confined to certain categories of depression.

Fig. 2 Base line 5-HIAA concentration in the CSF, and increase of this concentration after probenecid in the group of endogenous depressions, the group of neurotic depressions and the control group.
5. Central MA metabolism and antidepressant medication

Is the responsiveness or resistance of a patient to antidepressants related to the presence or absence of disorders in the cerebral MA metabolism? Do antidepressants (all potentiators of central MA-ergic activity, as already pointed out) abolish the supposed MA deficiency in the brain? So far, three studies have been devoted to this question and their results, although of a preliminary nature, certainly warrant further investigation of this hypothesis.

The first study I mention was made in Groningen (Van Praag et al. 1972). Of 10 patients with severe endogenous depressions five were treated with a placebo for three weeks, while five were given dl-5-hydroxytryptophan (5-HTP) – a 5-HT precursor which is transformed to 5-HT in the brain. The study was of double-blind design. The probenecid test was carried out in advance in all cases. The purpose was to test the hypothesis that, should 5-HTP have antidepressant properties, these would most likely become manifest in patients with a subnormal 5-HIAA response to probenecid. The five placebo patients showed no improvement. Of the five treated with 5-HTP, three showed improvement according to the physician in charge, the attending nurse, and themselves. In these three patients the 5-HIAA accumulation after probenecid had been subnormal. Of the two patients who did not improve, one had shown normal and the other had shown low-normal 5-HIAA accumulation (Tab. 3). The groups were too small to warrant definite conclusions but, to put it very prudently, these results are not inconsistent with the hypothesis that 5-HTP is an antidepressant and that 5-HIAA accumulation in the CSF after probenecid can be predictive of the chance of success of this medication.

![Fig. 3 Base line HVA concentration in the CSF, and increase of this concentration after probenecid in the group of endogenous depressions, the group of neurotic depressions and the control group.](image-url)
Gustafson et al. (1973) studied the question whether a relationship exists between the 5-HIAA concentration in the CSF and the therapeutic response to nortriptyline. They found that the latter was considerably less in the group of patients with a 5-HIAA level below 15 ng/ml than in those with a higher level. This in spite of the fact that the plasma nortriptyline level was well within the therapeutic range.

Nortriptyline is an antidepressant which differs in mechanism of action from the classical tricyclic compounds: imipramine (Tofranil) and amitriptyline (Tryptizol). For, rather than exerting an identical inhibitory influence on the re-uptake of catecholamines (NA and DA) and 5-HT, it shows a marked predilection for the catecholamine “pump”. The 5-HT re-uptake is much less markedly inhibited. To phrase it differently: nortriptyline centrally potentiates the activity of catecholamines much more intensively than that of 5-HT. It is conceivable that such a compound must lose some of its efficacy in patients in whom, as CSF studies show, it is precisely the 5-HT turnover that seems to be diminished.

The third study to be mentioned in this respect is that of Maas et al. (1972a), who demonstrated that patients who excreted relatively low levels of MHPG prior to treatment with imipramine or desmethylimipramine, responded better to treatment with these agents than did patients who excreted relatively higher levels of MHPG.

### 6. Towards a biochemical typology of depression?

A tentative answer can now be given to the three basic questions I posed in the introduction. In depressive patients the cerebral MA turnover can be diminished. These disorders do not occur in all patients but seem to be confined to certain categories of depression. Diminution or non-diminution of the central MA turnover is a factor which determines whether antidepressant medication will succeed or fail. A factor. Not the factor. The question why some patients do while others do not respond to antidepressants is a very complex one. Numerous factors are probably involved: the symptomatology of the depression; its aetiology; pharmacokinetic factors such as the patient’s ability to turn a given dose of an antidepressant into an adequate blood concentration. Of this complex question I have elucidated only one aspect: the metabolic. Can factors related to the central MA metabolism exert an influence on the therapeutic efficacy of antidepressants?

The fact that I am inclined to answer this question in the affirmative has theoretical and practical implications. Theoretical implications because it has been established that
MA-deficient and non-deficient patients are not always distinguishable on the basis of psychopathological symptoms. So far, we have been accustomed to using an aetiological and a symptomatological typology of depressions. The findings I have discussed would seem to suggest that a biochemical typology of depressions is among the possibilities.

The practical implications are two-fold. It is to be expected that biochemical factors will come to play a role in determining indications for antidepressant medication in the not too distant future. This would substantially enhance the rationale of prescribing antidepressant agents. Secondly, a biochemical typology of depressions could hardly be anything but a stimulus giving impetus to the search for antidepressants with a more specific action than those currently available. For the depressive patient, too, the future seems to hold the promise of the right drug for the right patient.

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