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ANTIDEPRESSANTS

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Antidepressants[1]

Depression is a common syndrome, especially in middle life (Silverman, 1968), and the treatment of depressed patients absorbs a large share of the professional effort of general physicians and psychiatrists alike. Although it is convenient to speak of the pharmacological treatment of depression, drugs are only components, though often the main ones, of total management. When we "treat" depression we really preside over its course. We try to guard our patients from death and lesser complications, and we try to hasten the remission process.

Several modalities can be used with or in place of drugs, electric convulsive treatment (ECT) being the most important. I regard psychotherapy as adjunctive to the management of the depressive attack, though it may be very important in fortifying the patient against later attacks. During the attack, psychotherapy and milieu therapy set the stage on which drugs play their part. The stage setting can, in fact, exert considerable importance, but I see no reason to rely on it exclusively. Antidepressant drugs, however, tend to show a troublesome latency in exerting their therapeutic effects, and it is during this period that the patient should be counseled about delay and reassured that treatment is in progress.

With the combined use of ultrafast and ultra brief barbiturates and

muscle relaxants, ECT has become both safer and less unpleasant. However, it remains cumbersome, and is a procedure best limited to hospitalized patients. At present, ECT rarely is used to commence treatment; it is generally reserved for patients who have not responded adequately to drugs, or for the rare patient for whom drugs are contraindicated. At our clinic, we do advocate its initial use for one type of patient, the agitated patient, often middle-aged and usually a man, who presents frank suicidal intention. We give ECT to such a patient as soon as necessary tests of physiological function are performed. We may give it daily until mental confusion supervenes and reduces the ability of the patient to carry out his suicidal drive.

Theoretical Considerations

In defending theory to clinicians, Fuller Albright-argued that rides can apply to only 90 percent of patients and that rigid adherence to rules will produce more harm in the remaining 10 percent than good in the majority to whom they apply. He recommended theory in place of rules.

In large measure, drugs have given us the notions by which our use of them is guided. Relying on drug effects and referring to our least important antidepressants, I shall state a theoretical position. Within this context I shall then discuss the use of our most ‘important antidepressants, the tricyclics.

In the phylogenetically old parts of the mammalian brain there are

found in high concentrations certain small molecules known as biogenic amines (Kety, 1967). They concentrate in nerve ends and are released by nerve impulses (Kopin, 1965). They enter the synaptic cleft, reach sensitive areas of the adjacent cell body, tend to alter its polarization, and thus influence the likelihood of transmission. The synthesis, storage, release, and inactivation of these substances are more or less complicated (Glowinski, 1972) and can be affected by drugs (Axelrod, 1966). The biogenic amines are of two chemical types: (1) catecholamines, i.e. dopamine (DA), norepinephrine (NE), and epinephrine; and (2) indoleamines, i.e., tryptamine (TA) and 5-hydroxytryptamine (5-HT, serotonin). With regard to depression, and probably mania as well, NE and 5-HT seem the most important.

Several authors have drawn attention to the importance of NE (Bunney, 1965; Prange, 1964), but Schildkraut (Schildkraut, 1965) has put the matter most lucidly by stating the catecholamine hypothesis of affective disorders: "Some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Elation conversely may be associated with an excess of such amines." The role of 5-HT has not been so formally stated, but several authors (Coppen, 1967; Glassman, 1969; Lapin, 1969) have garnered evidence suggesting that 5-HT activity is deficient in depression. These two hypotheses have provided considerable leverage for the understanding, chemical remedy, and further investigation of affective

disorders. However, they appear insufficient as theoretical positions, as I have tried to indicate elsewhere (Prange, 1972).

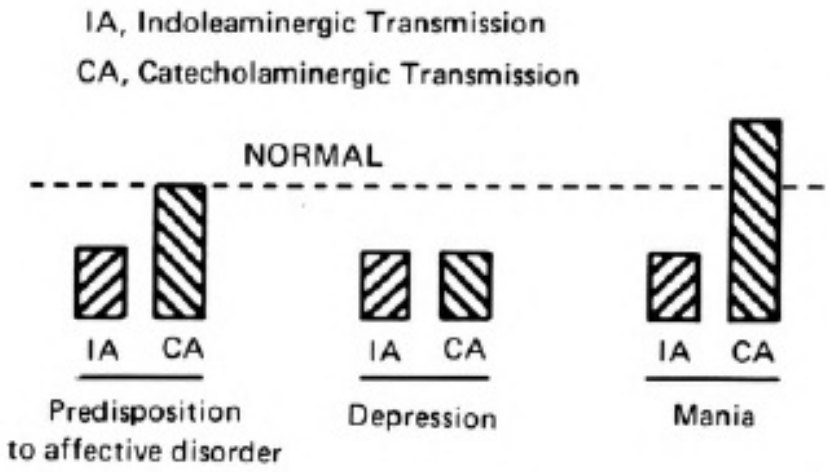
Several authors believe that we should broaden our focus to include receptor sensitivity as well as biogenic amine changes (Prange, 1972; Rosenblatt, 1969; Rosenblatt, 1969), since together they determine synaptic transmission. Moreover, we would be wise not to disregard cholinergic mechanisms, which govern most of the brain (Iversen, 1970). Janowsky et al. (1972) have for example shown that physostigmine, a cholinesterase inhibitor, has a remarkably prompt beneficial action in mania.

Even within the realm of biogenic amines there are unsolved problems. Chief among these is how to combine the catecholamine hypothesis and the indoleamine hypothesis. Kety (1971) made a suggestion that our group has stated formally (Prange, 1973): "A deficit in central indoleaminergic transmission permits affective disorder but is insufficient for its cause. Changes in central catecholaminergic transmission, when they occur in the context of a deficit in indoleaminergic transmission, act as a proximate cause for affective disorders and determine their quality, catecholaminergic transmission being elevated in mania and diminished in depression." This can reasonably be called *the biogenic amine permissive hypothesis of affective disorder,* or simply the *permissive hypothesis.* See Figure 23-1.

This unifying notion rests on the similarities between mania and depression, phenomenological (Court, 1968), physiological (Whybrow, 1969), chemical (Coppen, 1972) and pharmacological (Akimoto, 1960; Schou, 1957). In particular, the end product of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), seems diminished in cerebrospinal fluid in both mania and depression, and at least in depression the diminution persists after remission (Coppen, 1972). Agreement on these points, however, is far from perfect (Post, 1973).

With these thoughts in mind, we can profitably examine the mood-active substances listed below.

Figure 23-1.



Alterations in biogenic amines in affective disorders according to the

permissive hypothesis.

Mood-Active Substances

A. MAO Inhibitors

1. hydrazines
   e.g., phenelzine (Nardil)

2. non-hydrazines
   e.g., tranylcypromine (Parnate)

B. Tricyclics

1. nonsedating

   a. methylated
      e.g., imipramine (Tofranil)

   b. demethylated
      e.g., desipramine (Pertofran, Norpramin)

2. sedating

   a. C = C, ring to side-chain
      e.g., amitriptyline (Elavil)

   b. C = C, ring to side-chain; oxygen in ring
      e.g., doxepin (Sinequan)

C. Stimulants

1. potent but addicting
   e.g., d-amphetamine (Dexedrine)

2. non-addicting but impotent
   e.g., methylphenidate (Ritalin)

D. Lithium salts

E. Amino acids
   e.g., L-Dopa, L-tryptophan

F. Phenothiazines
   e.g., chlorpromazine (Thorazine)

Monoamine oxidase (MAO) inhibitors inhibit the enzyme monoamine oxidase. This enzyme inactivates biogenic amines within the nerve end. When we inactivate (with a drug) an inactivator (the enzyme), we increase the amount of biogenic amines ready for release upon receipt of the nerve impulse. The difficulty with MAO inhibitors, whether they are hydrazines or non-hydrazines, is the wide distribution of monoamine oxidase, or oxidases, in the body. Their substrate specificity and drug sensitivity may vary from tissue to tissue (Shih, 1971) and even within the brain (Fuller, 1970). However, if we inhibit one in the brain, we are likely to inhibit all in all sites, at least to some extent. As a consequence, the MAO-inhibited patient stands in toxic jeopardy. If he eats otherwise innocuous foods (Goldberg, 1964; Stockley, 1969), or if he ingests certain amine-active drugs (Goldberg, 1964;

Mason, 1962, Stockley, 1969; Tonks, 1965), including other antidepressants (Schuckit, 1971), he is subject to serious toxicity. Moreover, MAO inhibitors are inherently toxic, and several have therefore been removed from the U.S. market (Lifshitz, 1963). Probably the pharmacotherapy of depression should not begin with a MAO inhibitor unless the patient gives a clear history of excellent response during past attacks coupled with a history of poor response to tricyclics. The MAO inhibitors may reasonably be used, after a drug free interval, when tricyclics have failed.

It has recently been shown in man that MAO activity in the brain increases with age while biogenic amine levels diminish (Robison, 1972). This suggests that MAO inhibitors would be specific remedies for depression in elderly patients. While this idea is appealing, it does nothing to decrease the toxicity of these drugs. A related finding has been reported by Jones et al (Jones, 1972). These authors gave MAO inhibitors to moribund elderly patients. At autopsy they found that fixed doses of drugs had exerted extremely variable effects on the brain enzyme.

Stimulants, lithium salts, amino acids, and phenothiazines can also be dealt with summarily. The stimulants appear to be not so much antidepressants as psychomotor activators. While some of them, notably amphetamine, may induce a degree of euphoria in normal subjects, depressed patients may perceive their action as unpleasant. The stimulants tend to be

either potent and addicting or, on the other hand, non-addicting but impotent. Amphetamine causes the prompt release of NE and DA from nerve ends (Carr, 1969; Glowinski, 1966).

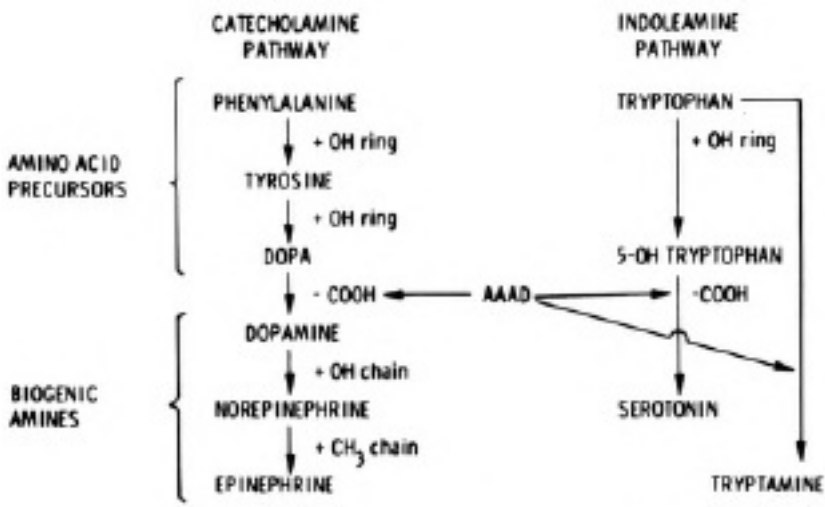
Lithium salts, principally the carbonate, are used to control manic attacks (Schou, 1957; Davis, 1973). They probably reduce the incidence of manic recurrence (Baastrup, 1970) and may also diminish the incidence of depressive relapse (Coppen, 1971). One would expect this effect to be especially manifest in bipolar patients prone to recurrent depression. However, Coppen et al. (Coppen, 1971) found that lithium prevented the recurrence of unipolar and bipolar depressions about equally. Lithium may be effective in some depressive attacks (Dyson, 1968), but this is uncertain. Lithium, through a number of complex actions, decreases brain NE activity (Schildkraut, 1966) and increases brain 5-HT activity (Sheard, 1960, Tagliamonte, 1971). According to the permissive hypothesis, we should expect lithium to remove "permission" for both mania and depression. By reducing NE activity it should be an excellent treatment for mania but might be less effective or even fail in depression, depending on the balance of its effects.

L-Dopa is an amino acid precursor of catecholamines (see Figure 23-2). When ingested in large amounts it produces a rise in brain catecholamines, DA more than NE (Hornykiewicz, 1970). Its use has led to great progress in

the management of Parkinson's disease (Keenan, 1970). In this disorder L-Dopa can produce a medley of mental effects or none at all (Barbeau, 1971; Yaryura-Tobias, 1970). It seems to have antidepressant value in only a few depressed patients (Bunney, 1970), and they have not yet been identified prospectively. The antidepressant value of L-Dopa is unreliable and I have cited this as a criticism of the catecholamine hypothesis (Prange, 1964).

The effects of L-Dopa are, however, consistent with the permissive hypothesis. By increasing catecholamine activity without increasing indoleamine activity L-Dopa might only change the sign of affective disorder, and indeed swings from depression to mania during L-Dopa treatment have been reported (Murphy, 1971). Moreover, L-Dopa probably reduces central indoleamine activity, quite apart from failing to increase it. After administration of L-Dopa there is a sharp drop in cerebrospinal fluid levels of 5-HIAA (Goodwin, 1971). Amino acids compete for transport into cells," and an excess of one precursor may exclude others. Moreover, L-Dopa requires only the ubiquitous enzyme, aromatic amino acid decarboxylase (AAAD), to be transformed to the active amine DA, which may displace 5-HT, thus acting as a false transmitter (Kopin, 1965).

Figure 23-2.



Synthetic pathways of biogenic amines.

L-tryptophan (L-TP) is a more physiological substance to use as a precursor than L-Dopa and, for that matter, more physiological than 5-hydroxytryptophan (5-HTP). L-TP requires the discretely localized tryptophan hydroxylase to be converted to 5-HT. Thus, a loading dose of L-TP is unlikely to lead to the formation of 5-HT where it does not normally occur. The possibility must be kept in mind, however, that L-TP may be widely decarboxylated to TA, and that this substance could displace other amines. However, this may not occur to an important degree. Dunner and Goodwin (1972) have shown that in man a L-TP loading dose causes only a slight decrement in cerebrospinal fluid homovanillic acid, the end product of DA

metabolism, while the decrease of 5-HIAA after L-Dopa is substantial.

The effects of 5-HTP administration are often compared directly to the effects of L-TP administration. Each procedure may yield its own species of information and the two may be usefully compared, but they are not equivalent procedures. Figure 23-2 shows that 5-HTP can form only 5-HT but, as mentioned, it can form this substance anywhere that AAAD occurs. On the other hand, L-TP can form 5-HT only where tryptophan hydroxylase and AAAD occur together, i.e., in physiological locations. It is interesting to note, however, that pyridoxine, an AAAD cofactor, seems to have an important influence on the effects of L-TP. Under Hall's leadership, our group showed that neither L-TP nor pyridoxine alone has any effect in Parkinson's disease, while the combination markedly aggravates this condition (1972). From this it appears that TA formation may, after all, be important, whether as a physiological or as a false transmitter. It should be recalled that Dewhurst (1965) has based a biochemical theory of affective disorder partly on alterations in TA metabolism. The theory was criticized in part on the ground that TA was difficult to identify in mammalian brain even after L-TP loading and MAO inhibition (Eccleston, 1966). Although other criticisms remain (Weil-Malherbe, 1968), this objection was largely removed when Saavedra and Axelrod (1972), using a sensitive method, identified TA in the brains of untreated rats.

Coppen and his colleagues have found that L-TP with pyridoxine is an effective treatment for depression whether (Coppen, 1963) or not (Coppen, 1972) an MAO inhibitor is given concomitantly. Pare (Pare, 1963) and Glassman and Platman (1969) confirmed this response when an MAO inhibitor is used, and Broadhurst (1970) confirmed the finding when the drug is omitted. On the other hand, Bunney et al. (1971), and Carroll et al. (1970) found that the amino acid without an MAO inhibitor is ineffective. These discrepancies may reflect differential responses of unipolar and bipolar patients (Goodwin, 1973). Results with 5-HTP are uniformly disappointing in depression (Glassman, personal communication; Glowinski, 1966).

According to the permissive hypothesis, L-TP should be a better treatment for mania than for depression. In depression, a 5-HT increment would be beneficial but an NE decrement (from L-TP crowding out endogenous L-Dopa) could be harmful. In mania, on the other hand, both actions of L-TP would be beneficial. To test these notions, we treated ten patients with moderately severe mania with a small dose of L-TP (plus pyridoxine), then chlorpromazine or the substances in reverse order (Wilson, 1973). We found L-TP superior. Its advantage was clearest in, but not limited to, the control of activity. We suggested that the motor phenomena of mania and the agitation of depression, when it is present, may form a connecting link between the two disorders. Kotin and Goodwin (1972) recently reappraised the notion that the mental content of depression may be present

during mania. Our concept concerning motor phenomena is analogous.

It is instructive to compare L-TP and lithium in the treatment of affective disorders. The former appears to be useful in depression and in mania, while lithium is useful in mania and may be in depression. This similarity of clinical activity seems quite likely related to the two substances sharing both "proindoleaminergic" and "anti catecholaminergic" properties. It is of parenthetical interest that in preliminary work our group has found both substances useful in the treatment of tardive dyskinesia (Prange, 1973), and that Dalen (1973) has confirmed the value of lithium.

Phenothiazines have been reported to exert antidepressant effects. These appear limited to agitated depressions (Hollister, 1965), perhaps to the agitation aspects of depression. Since phenothiazines are also useful in mania (Lehmann, 1954), this nexus of observations may support the notion that motor phenomena form a link between mania and depression.

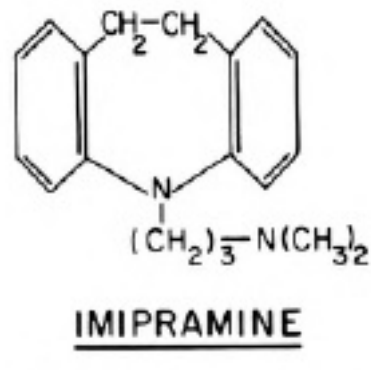
A View of Drug Treatment

Tricyclics are the most important antidepressant drugs; imipramine is the prototype of this class. Imipramine is not the best tricyclic for all patients but it is the standard to which others are compared.

Figure 23-3 shows the chemical structure of imipramine, as a point of

reference, and Table 23-1 characterizes the chemical differences between the six tricyclic antidepressants currently available to physicians in the United States. The tricyclics differ from the phenothiazines and the thioxanthenes by having seven rather than six atoms in the central ring. The ring in doxepin contains an oxygen atom. All tricyclics are tertiary or secondary amines; some have double bonds between the central ring and the side chain. These differences in molecular structure are only poorly correlated with differences in clinical activity. Klerman and Cole (1965) and Gyermek (1966) have given full accounts of the pharmacology of imipramine.

Figure 23-3.



The molecular structure of imipramine.

The mechanism of action of tricyclics was an enigma and their clinical efficacy was troublesome to theorists of affective disorders until Hertting et

al. (1961) showed that imipramine blocks the reuptake of NE into the nerve end following its release. Inactivation by reuptake is probably the major physiological means of terminating the action of both NE (Kopin, 1965) and 5-HT (Roth, 1959). Thus, by showing an action of a tricyclic on NE which would prolong the fife of the amine in the synaptic cleft, Hertting et al. solved an enigma and gave powerful support to the catecholamine hypothesis. The matter is probably more complicated than it first appeared, as Schildkraut suggested, and his later findings may help explain the clinical latency of tricyclic antidepressant action (1972).

Reuptake blockade by tricyclics is not limited to NE but pertains as well to 5-HT. A series of elegant studies have demonstrated that tricyclics which are tertiary amines block mainly the reuptake inactivation of 5-HT; tricyclics which are secondary amines block mainly the reuptake inactivation of NE (Lidbrink, 1971). It is a criticism of the single-amine hypotheses of affective disorders that imipramine, a tertiary amine, and desipramine, a secondary amine, are equally effective clinically in unselected patients (Klein, 1969).

The notion was widely held that imipramine, with a side chain containing two terminal methyl groups and which is, therefore, a tertiary amine, had to be partly demethylated in the body to become an active antidepressant. Since slow onset of action was a drawback of imipramine, the demethylated product, desipramine, was synthesized in the hope that it

would be a faster-acting drug. The data, however, that have been adduced to demonstrate that desipramine acts faster than imipramine, or that nortriptyline acts faster than amitriptyline are not persuasive (Klein, 1969). Tertiary amine tricyclics are now considered to be active substances themselves.

An important difference was produced when a carbon atom was substituted for the nitrogen atom in the central ring of imipramine and when it was linked to the first side-chain carbon by a double bond. The result was amitriptyline (see Table 23-1). Amitriptyline is more sedating than imipramine or desipramine and so are its congeners, doxepin and nortriptyline. Amitriptyline, doxepin and nortriptyline, in addition to their sedative properties, possess anxiolytic properties, but so does imipramine and, for that matter, desipramine. The distinguishing feature of the newer tricyclic drugs, then, is primarily their sedative properties and only secondarily their anxiolytic properties. Doxepin may be an exception, for its tranquilizing effect has been compared favorably with that of chlordiazepoxide (Sterlin, 1970). Protriptyline, on the other hand, is a stimulating agent. It is remarkable that all tricyclics, with the exception of protriptyline and the partial exception of nortriptyline, are about equally potent on a weight basis, and that their dose range is so narrow, barely threefold, compared to that of other psychotropic drugs.

Choice of a Drug

Tricyclic antidepressants have more similarities than differences. If this is true, it follows that choosing between them is difficult but often unimportant. In making a choice, depressive typology is often used as a guide.

Characteristics of Chemical Structure in Antidepressants

CHARACTERISTICS	IMP	AMI	DOX	DMI	NOR	PRO
Tertiary amine	X	X	X			
Secondary amine				X	X	X
Ring-to-side-chain bond						
nitrogen-to-carbon						
single bond	X			X		
carbon-to-carbon						
single bond						X
double bond		X	X		X	
Oxygen in central ring			X			

Legend: IMP = imipramine; AMI = amitriptyline; DOX = doxepin; DMI = desipramine; NOR = nortriptyline; PRO = protriptyline.

If one classifies depressed patients as neurotic or psychotic, implying that the neurotic is less depressed but more likely to show anxiety, then a

drug with sedating properties is more likely to be useful in neurotic depression. If a contrast is made between agitated and retarded patients, it is the former who are more apt to profit from a phenothiazine than the latter, though imipramine is an effective remedy for both (Prange, 1969; Wilson, 1970). If one refers to history rather than description of the current attack, a unipolar-bipolar dichotomy can be made. It is in bipolar depression that lithium may be of some value, though even here it is probably less useful than more accepted treatments, such as imipramine. It is of theoretical interest, but little practical help, to know that bipolar patients are more likely than unipolar patients to respond to L-Dopa (Murphy, 1971) and to imipramine (Coppen, 1972) with hypomanic excursions. Perhaps this phenomenon includes most other antidepressant agents as well. If the permissive theory is accurate, however, L-TP should not produce hypomania. Coppen et al. (1972) did not observe it in a small series of patients.

The endogenous-reactive dichotomy is not useful, in my experience, as a guideline in choosing a drug, let alone in choosing between tricyclics. Some clinicians employ it, but I think they are responding to information that more aptly pertains to severity or to a neurotic-psychotic dichotomy. In any case, patients tend to become "more reactive" as their history unfolds. To the extent that patients can be assigned to one or the other moiety, endogenously depressed patients do seem to respond better to drugs.

If choosing a drug by clinical characteristics is risky, choosing one according to psychodynamics is dangerous. It can even lead to the selection of a drug from the wrong class of psychotropics. If, for example, a middle-aged woman has sustained a series of object losses but presents manifest anxiety, not depression, and if she needs a psychotropic drug, it is an anxiolytic, not an antidepressant. Chemical characteristics of the patient are no more valuable in drug selection, though Schildkraut et al. (1971) have suggested in a preliminary study that amitriptyline is more useful than imipramine in patients who show high excretion rates of 3-methoxy-4-hydroxy phenyl glycol.

Some of the obvious differences between depressed patients are somewhat helpful in drug selection. A few patients are men while most are women (Silverman, 1968), and we have found that men respond better than women to imipramine (Prange, 1972). While this may serve as an investigational lead, it does not tell us what to prescribe for a specific woman. Just as obviously some depressed patients are elderly, while most are middle-aged (Silverman, 1968). This observation also does not help us to choose drugs according to their therapeutic qualities, though Klein and Davis (1969) suggested that differences between studies by Sandifer et al. (1965) and by Hordern et al. (1963) can be understood by assuming from Hordern's evidence that amitriptyline is a more effective drug in the aged than imipramine. The consideration of age introduces a complementary approach,

i.e., choosing between tricyclics according to side effects.

Side Effects

Tricyclics cannot be classified more sharply according to side effects than according to therapeutic effects. Nevertheless, a consideration of both can often lead to the rational choice of a tricyclic for a given patient. Sedation offers a convenient link between the two types of drug effects. Sedation, like many drug effects, is therapeutic when we desire it and a nuisance when we do not.

All tricyclic drugs exert anticholinergic actions. They produce dry mouth, which is generally only a transient nuisance, and minor cardiovascular effects such as palpitations and tachycardia. Orthostatic hypotension is less common. Tricyclics may also produce toxic confusion and urinary retention, and may aggravate glaucoma.

These side effects are most apt to occur and to be serious in elderly patients. For this reason a drug that seems to have a somewhat reduced anticholinergic potential, such as doxepin (Ayd, 1971), may be of special value in the elderly when other considerations do not countervail. For related reasons the elderly are rarely given full doses of tricyclics, unless they are gradually attained while side effects are watched. It is probably unwise to give an elderly patient his entire daily dosage at bedtime (Prange, 1973), as

has been recommended for younger patients (Klein, 1969).

The cardiovascular effects of tricyclics are probably due not only to their anticholinergic properties but also to their ability to block the reuptake inactivation of NE and 5-HT. The responses of a given patient probably represent the sum of these various actions. Amine theories of affective disorders depend mostly on the observation that tricyclics prolong or intensify the activity of released biogenic amines. This occurs in the periphery (Hertting, 1961), as well as in the brain (Glowinski, 1964). Therefore one would expect hypertension, not orthostatic hypotension, to be a consequence of tricyclic administration. Indeed, hypertensive events have been related to imipramine ingestion (Hessov, 1970), though orthostatic hypotension is much more frequent. Another hypothesis derived from current theory in its simplest form is this: depression and hypertension are incompatible disorders, i.e., one cannot suffer from a lack of amines and from their excessive presence at the same time. In fact, depression and hypertension frequently do coexist and this combination in a given patient tests the pharmaco-therapist. Were it not for the variety of antihypertensive drugs such patients are usually taking, one might regularly recommend the cautious use of pargyline, an MAO inhibitor which may have been used in the psychiatric rather than the antihypertensive clinic, had not MAO inhibitors fallen into disfavor with psychiatrists. The main alternative to drugs, ECT, should be reconsidered in this situation.

Remaining Problems

The foregoing is relevant mainly to the 75 percent of depressed patients who respond favorably to a program of treatment centered around currently available antidepressant drugs. The refractory 25 percent are but one of the problems in this field, and I will return to them after taking up some other issues.

The physician is never presented with a *depressed* patient, only with a patient. He must make his own diagnosis. This depends upon recognition, which in turn depends upon suspicion. Diagnosis, though often easy, is sometimes difficult. I refer to what an earlier generation of psychiatrists termed "depressive equivalents" (Earley, 1956; Mendels, 1970) I do not mean, for example, the patient who is manifestly anxious but demonstrates the psychodynamic constellation usually associated with depression. I refer to the patient who presents somatic complaints, usually vague but persistent, seems gloomy, verbalizes poorly, and may present a history that typically is antecedent to depression. I do not think these patients, who are the bane of both the general physician and the psychiatrist, respond very favorably to antidepressant drugs. A trial of one such drug, however, is at least as rational as the variety of drugs that generally have previously been directed to this or that complaint.

The general physician, as much as the psychiatrist, must remember that

depression of serious, even suicidal, proportions can be present even when it is not the chief complaint. The medical profession needs to be reminded of this periodically, Fawcett (1972) has performed this service most recently.

Another problem, as I have indicated, is the need for a subclassification of patients with manifest depression that would serve as a guide to drug treatment. I have mentioned a few guidelines, but they are of limited practical value. The unipolar-bipolar dichotomy seems reliable and appears to tally with a number of physiological distinctions (Dunner, 1971). It offers little predictive leverage on drug treatment, however, and even if it did we would not have advanced very far. The vast majority of depressed patients fall in the unipolar group, and we would still need to distinguish between them. It is possible, of course, that no valid distinctions exist. Conceivably all, or nearly all, the variations in depression to which we are witness are idiosyncratic elaborations of a basic, more or less uniform midbrain dysfunction variously achieved. If this is true, we should seek more nearly universal remedies and in the meantime try to enhance by milieu therapy or any other means the remedies at hand. I have no convictions about the venerable problem of typology (Kendell, 1968; Mendels, 1970; Mendels, 1968; Roth, 1959; Sandifer, 1966). In fact, if broad diagnostic criteria are applied, many depressions are atypical (Roth, 1959).

Although it would be a convenience for the theorist if anxiety and

depression did not coexist, in fact they often do. With drugs one tries to treat the dominant constellation of symptoms. An antidepressant with sedative-anxiolytic properties is indicated if depression seems uppermost. When the symptoms of anxiety and depression are nearly counterbalanced a drug combination becomes advisable. A tricyclic and a phenothiazine, for example, can be useful, but their combination should be reserved for this specific instance and not routinely prescribed with a "just in case" attitude. There is an advantage in starting drugs a few days apart to learn, if possible, some of the wanted and unwanted effects of the first before confounding the clinical situation with the second.

Various adjuncts have been used to accelerate the clinical action of tricyclics. Our group has found that the addition of a small amount of L-triiodothyronine (T3) to a usual tricyclic regimen is effective (Prange, 1972; Wilson, 1970), at least in women (Prange, 1972). This has been confirmed by Wheatley (1972) and by Coppen et al. (1972) but not by Feighner et al (1972). Methylphenidate appears to be effective (Wharton, 1971). This drug interferes with the enzymatic destruction of imipramine (Perel, 1970) and thus given doses of tricyclic produce higher tissue levels.

What can one do about depressed patients who are refractory to usual drug programs? The first approach is to insure adequate dosage. Some previously unresponsive patients respond if they are given 250-300 mg. of

imipramine or its equivalent. Side effects are more or less related to dosage, however, and one should watch for them carefully (Wilson, 1963). An alternative is to administer ECT. In my opinion, exclusive reliance on drugs is not sensible in the management of depression.

There are, of course, several pharmacological means of dealing with the refractory patient. In England, MAO inhibitors have been combined with tricyclics in the treatment of patients who failed on either class of drugs alone (Gander, 1966). Weight gain was striking, but toxicity was slight. Recently, Schuckit et al. (Schuckit, 1971) have challenged the notion—refuted it, perhaps— that MAO inhibitors and tricyclics, given in usual doses, are intolerably toxic. They indicated the need for more research on this point. However, it bears repetition that MAO inhibitors are toxic drugs, inherently as well as interactively, and the simultaneous use of a tricyclic cannot reduce this hazard. Reserpine and tetrabenazine can be added to imipramine treatment. In animals this causes excitement while reserpine alone causes lethargy (Sulser, 1960). In depressed patients it can correct refractoriness but it is accompanied by cardiovascular toxicity (Dick, 1966).

Earle (1970), in a single-blind study, gave T3 to depressed patients who had not responded to one or another tricyclic; most responded favorably. It is also worth mentioning that while we have shown that T3 accelerates imipramine response only in women, it is possible that it is useful in the

occasional man who is imipramine-refractory.

Finally, the question arises as to how long to continue tricyclic treatment. Information on this point is insufficient, but it seems reasonable to attempt dose reduction one month after remission is complete, reinstating full doses if symptoms recur. It is accepted practice to give half doses for six months after remission (Klein, 1969).

Concluding Remarks

Drugs are useful in the management of depression. The most useful are the tricyclics. Various means are available to accelerate their effects and to treat the patient who is refractory to usual regimens. Sound practice depends upon sound theory. Knowledge about drugs has contributed substantially to theories about affective disorders, and theory should guide drug administration.

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Notes

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