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DEPRESSION: SOMATIC TREATMENT METHODS, COMPLICATIONS - FAILURES

by

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Diagnosis and the Different Treatment Options of Depression.

One recognizes depression by one or all of the following three methods:

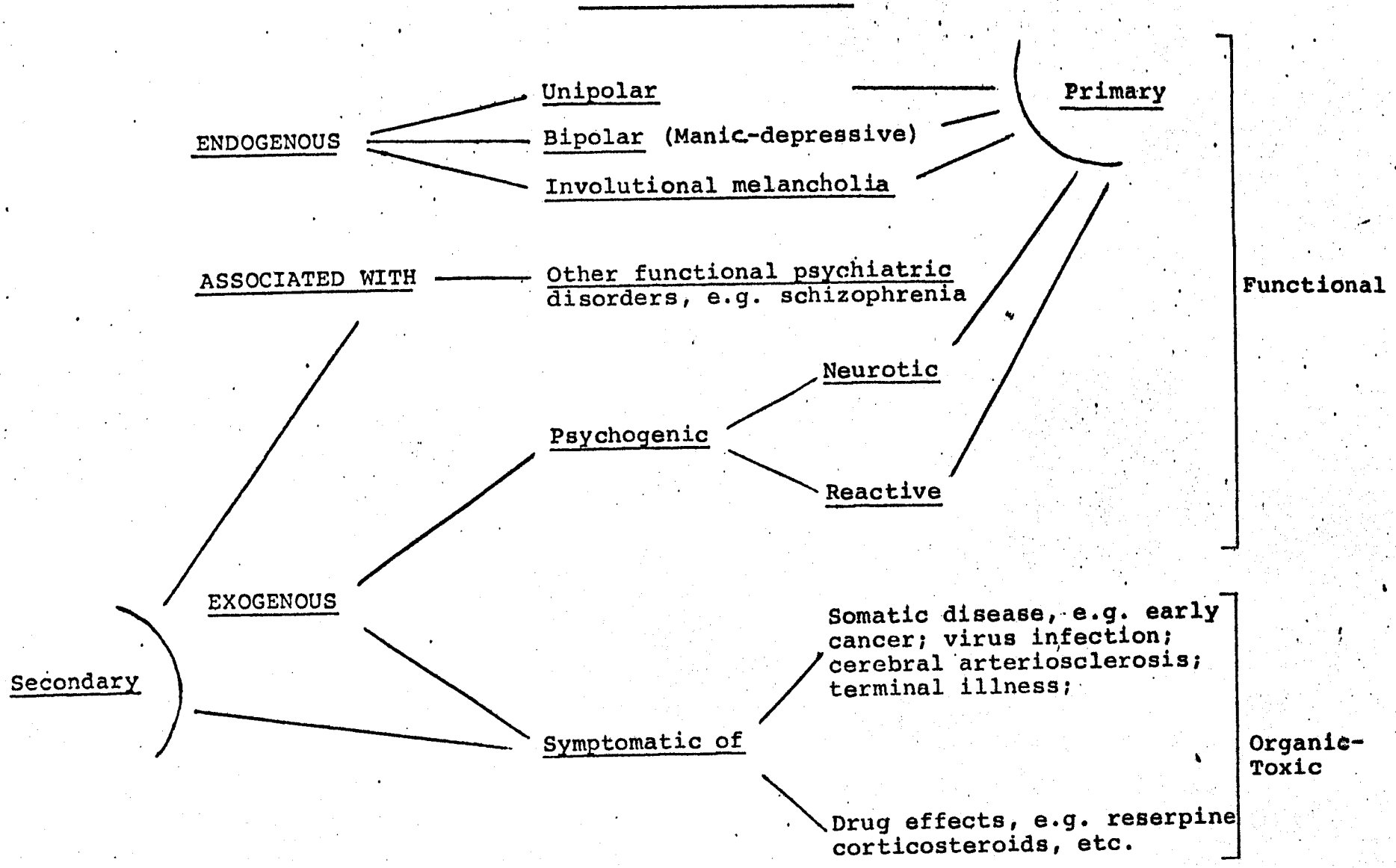
1. Observation
2. History
3. Empathy

The first two are basic for the diagnosis of any pathology and are thus shared by all of medicine. The third - empathy - is a diagnostic approach that is specific for the psychiatrist and has to substitute for the important third diagnostic method that is available to most physicians, but not to psychiatrists, that is, objective instrumental and laboratory findings. A nosological survey of current diagnostic concepts of depression is presented in Fig. 1.

Once he has recognized that his patient is depressed, the psychiatrist has to ask himself the following strategic questions, approximately in the given order:

1. Is the depression pathological or is it a grief reaction or plain unhappiness?
2. Does the patient require treatment?
3. Does he require hospitalization?
4. Is the depression primary or secondary?
5. Is he suffering from an endogenous or a psychogenic depression?
6. What treatment should the patient receive?
7. Will he require maintenance treatment?

Fig.1


AFFECTIVE DISORDERS
Primary
Unipolar
ENDOGENOUS
Bipolar (Manic-depressive)
Involutional melancholia
ASSOCIATED WITH
Other functional psychiatric disorders, e.g. schizophrenia
Functional
Neurotic
Psychogenic
Reactive
Secondary
EXOGENOUS
Somatic disease, e.g. early cancer; virus infection; cerebral arteriosclerosis; terminal illness;
Symptomatic of
Organic-Toxic
Drug effects, e.g. reserpine corticosteroids, etc.

Legend to Fig. 1

Nosological schema of affective disorders.

Answers to questions No.1, 2 and 3 will be based, on the patient's history or on the intensity of his symptoms. Questions No.4 and 5 will have to be answered partly on the basis of the history, i.e. the presence or absence of a time-related traumatic event (loss), or of a previous non-affective psychiatric disorder; and partly on the basis of existing symptoms, e.g. diurnal variation, early morning insomnia, or the presence of symptoms characteristic of a non-affective psychiatric disorder.

Finally, the answers to questions 6 and 7 depend to considerable extent on the answers to the other questions and, if it has been decided to use somatic antidepressant therapy, the different options will be discussed in this paper.

The psychiatric treatment of depression may be divided into three historic phases. During the first phase psychotherapy was sometimes helpful, but all somatic treatments were hardly any more than ineffective nostrums. Many of the old physical treatments of depression we would/consider to be cruel, aversive procedures; for instance, painful cold showers, unexpectedly being plunged into deep water or being whirled around while being strapped into a machine until severe vomiting and weakness set in. (Pinel, 1792; Reil, 1803; Cox, 1804). The second phase began in the late 1930's, when metrazol- and electroconvulsive therapy and, to some extent, psychosurgery, provided the first effective physical treatments of depressions. The third phase - that of modern pharmacotherapy of depression - began about 20 years later.

Table I gives the repertoire of somatic treatment modalities that are available today for the management of depressive syndromes. Although pharmacotherapy is currently the treatment of first choice of the experts, and by far the most widely used form of antidepressant treatment, (Klein, 1975) its discussion will be left to the end, and the other somatic treatments will be dealt with first.

Table I

Somatic Treatment Modalities for the Management of Depression

1. Pharmacotherapy
2. Sleep Deprivation
3. Electro-Convulsive Treatment (ECT)
4. Psychosurgery

Electroconvulsive Therapy (ECT)

(ECT is the physical treatment in psychiatry that has survived for almost 40 years, although we do not yet have any plausible theory of its action mechanism. (Hurwitz, 1974). It is the most effective treatment for depression. Curiously, it is also an excellent treatment for manic states and is helpful in many schizophrenic conditions. It is contraindicated in anxiety and hysterical states, as well as in brain-damaged patients. One of its drawbacks is the susceptibility to frequent relapses of patients treated with convulsive therapy.

The other main disadvantage of ECT is the memory impairment that invariably occurs after a few treatments. ECT produces a short-lasting acute brain syndrome with confusion, memory disturbances, disinhibition of affect, and slowing of the EEG. These symptoms are reversible and usually disappear completely within two to four weeks after the last treatment. However, in older people some permanent memory impairment may be observed. A more subtle, persistent memory disorder, that may not appear on tests, but may be disturbing to patients who depend much on their intellectual organization, can also occasionally be observed in younger persons. Unilateral ECT, administered over the non-dominant hemisphere, causes less memory impairment, but is possibly also somewhat less effective. (Levy, 1968).

ECT may be the treatment of choice in very severe and suicidal depressions, when it might be dangerous and intolerable for the patient to have to wait one or two weeks for the effects of antidepressant drugs to occur. It is also indicated in depressed patients who are not responding to antidepressant drugs within a month or two.)

A recent survey in Massachusetts has shown clearly that in private hospitals ECT is administered much more frequently than in state hospitals. (Diepz, 1975). This may be due to the fact that in private hospitals more nursing staff and anesthetists are available, in contrast to the more restricted economics prevailing in state hospitals; it may be a question of fees for service available in private but not in state hospitals; or it may reflect a greater need in private hospitals to see quick, dramatic and gratifying results. For with ECT, the first signs of improvement appear rapidly and are subjective: the patient feels well and immediately acknowledges this gratefully, even while his objective test performance is still impaired. With antidepressant drug treatment, the improvement is slower and first noticeable objectively in the patients behaviour. The patient himself may not acknowledge that he feels any better and does so, often somewhat grudgingly, only later.

To some clinicians it is a drawback of ECT that the patient recovers so rapidly and with such complete amnesia that he has virtually no recollection of becoming sick or getting well. He accepts good-humoredly that he must have been sick - or he would not have received the treatment - but the experiences of becoming ill and becoming well again, for what they are worth, are not available to him, and he will not be able to draw on what he may have learned from them, should he ever be threatened with a recurrence of his illness at some later time.

Sleep Deprivation

Sleep deprivation is a new antidepressant treatment modality that has been developed during the last three years in Germany. (Pflug, 1972). It consists in keeping the depressed patient awake continuously for 36 hours. The procedure may be carried out once or twice a week and, if the first

two treatments have been successful, may be repeated six or seven times. At our hospital we have had amazing success with sleep deprivation in 9 of 15 severely depressed, hospitalized patients who had not responded to antidepressant drug therapy. (Cole and Müller, 1975). In certain cases the results were as dramatic as with ECT.

The action mechanism of this unspecific procedure is not well understood. It is the converse of continous sleep, which was one of the first successful somatic treatments used in psychiatry. (Klaesi, 1922). Stress-induced stimulation of the adrenergic system may be involved in sleep deprivation, with the resulting metabolic and endocrine changes. It has also been demonstrated recently that REM sleep deprivation has a favourable influence on depression, a factor that may enter into the picture of sleep deprivation. Total sleep deprivation, like REM sleep deprivation, is only effective in endogenous, particularly unipolar, and not in reactive or neurotic depressions. (Bhanji and Roy, 1975).

Psychosurgery

Psychosurgery has today become the target of emotionally charged political attacks by vocal activists who clamor for its being outlawed protesting that psychosurgery constitutes "murder of the soul", that it may be used as a weapon against helpless minorities, AND that it reduces its "victims" to "vegetables". Without wishing to enter into the controversy, this writer must state that a thorough review of the literature and his personal clinical experience have convinced him that modern psychosurgery can be a valuable therapeutic weapon and, in certain desperate cases, may constitute the only effective relief available. In the 1930's and 40's, when its technique was still rather primitive and its use often indiscriminate, there were indeed many therapeutic failures and disastrous complications. Today, with stereotactic techniques, and used only for its restricted indications, one should expect 60-70 percent therapeutic successes, with very few physical complications and virtually no gross psychological deterioration, following psychosurgery. The only indications

for the use of psychosurgery are, in the writer's opinion: severe depression, anxiety, or obsessive-compulsive symptoms that have persisted for at least two years and have not been relieved by adequate treatment with any other available therapeutic methods, i.e. psychotherapy, pharmacotherapy and ECT. In other words, psychosurgery should only be used as a last resort and for some specific symptomatology in the relatively few cases where these qualifications apply. (Ostrow, and / Lehmann, 1973). While it is true that there is a dearth of controlled trials of psychosurgery, some retrospective studies with matched controls, and even one placebo-controlled experiment - only skin incisions under anesthesia - have been reported and have clearly shown the therapeutic value of psychosurgery when performed under the right conditions. (Livingston, 1953; Tan et al, 1971).

Pharmacotherapy

Many drugs had been used in treating depressed patients before modern antidepressant substances were introduced. Drugs used in past centuries include hellebore and opium, and more recently hematoporphyrin (Steinberg, 1936), dinitrile succinate (Gillis and Salfield, 1953) and nicotinic acid (Washburne, 1950). Of these, only the treatment with tincture opii found general acceptance and probably did give severely depressed patients some modest relief. However, reliably effective pharmacotherapy of depression became available only with the almost simultaneous discovery of the moncamine oxidase inhibitors and the tricyclic antidepressants in the late 1950's.

Monoamine Oxidase Inhibitors (MAOI's)

Since Kline (1958) introduced iproniazide into antidepressant therapy, a great deal of research has been centered on the MAOI's and their effects of increasing the biogenic indole and catecholamines and their metabolites in the brain, since this increase seems to be associated with an antidepressive action.

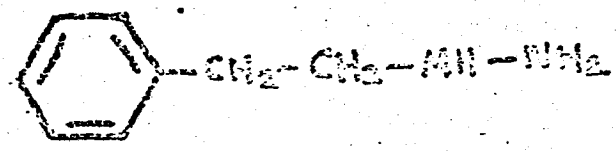
The pharmaceutical industry has developed two classes of MAOI's: those with and those without a hydrazide complex in their structure. The first MAIO - iproniazide (Marsilid) - was a hydrazide compound and proved to be hepatotoxic. Because of several fatal complications which occurred with its use, iproniazide was eventually withdrawn from the market in the U.S. This has been regretted by many psychiatrists who claim that iproniazide was probably the most effective of the MAOI antidepressants. Other, less toxic MAOI's, possessing hydrazide groups in their structure, include isocarboxacide (Marplan), nialamide (niamide) and phenelzine (Nardil). Tranylcypromine (Parnate) is an MAO without a hydrazide group, which is characterized by a biphasic action: an immediate stimulating and mood-lifting, amphetamine-like effect and a delayed, more gradual and sustained antidepressant action which appears after the typical 8-10 days that are required for most antidepressant drugs to take effect. (See Fig.2. for the chemical structure of some MAOI's.)

The therapeutic efficacy of MAOI's is probably about the same as that of other (tricyclic) antidepressants, i.e. from 60-70 percent improvement in unselected cases of depression. However, it has been frequently claimed that the MAOI's are specifically indicated in the more atypical depressions when hysterical, impulsive, obsessive, anhedonic and phobic symptoms prevail. (Alexander and Berkeley, 1959; Crisp et al, 1961; Kiloh et al, 1962; Sargant, 1962; West and Dally, 1959). This clinical impression has not been confirmed in some controlled studies (Spear et al, 1964; Leitch and Seager, 1963), and many clinicians have seen the same type of depression also respond well to antidepressants other than MAOI's.

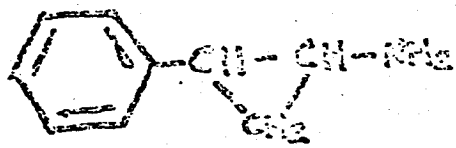
One serious inconvenience of all MAOI's is their incompatibility - and often intensely adverse interaction, in the form of paroxysmal hypertension - with adrenaline, noradrenaline and practically all adrenergic drugs, such as

Fig. 2

MAO - INHIBITORS



PHENELZINE



TRANYLCYPROMINE

the amphetamines, methylphenidate, etc., but also with alcohol, thyroxin, meperidine, tricyclic antidepressants, and many food items which contain tyramine, a noradrenaline - releaser. Unfortunately, such food items comprise a great variety of the common diet, e.g. aged cheeses, pickles, chicken livers, beer, Chianti wine, etc. A sudden surgical emergency in a patient who is on MAOI treatment, may present problems to the anesthesist because of the many interactions and the long sustained actions of MAOI's with other drugs; even a local anesthetic for dental procedures would be contraindicated, if it would be used together with epinephrine.

As a general rule, one should remember to prescribe MAOI's only to patients who are sufficiently intelligent and reliable to adhere to all the warnings and instructions, which must necessarily be made very explicit to all patients for whom this type of drug is prescribed. Special caution is indicated with young persons who might be suspected of being multiple-drug abusers.

If a patient has been started on an MAOI and it has been decided to change to tricyclic antidepressants, 8 to 10 days must be allowed to elapse before the new medication can be prescribed, since the drugs' inhibition of MAO is irreversible, and it takes about a week before a sufficient amount of new MAO enzyme has been produced by the organism.

Daily doses of MAOI antidepressants marketed in the U.S. are listed on Table II.

Tricyclic Antidepressants

The prototype of the tricyclic antidepressants is imipramine (Tofranil) whose antidepressant properties were first discovered and reported by Kuhn (1957). Chemically, the tricyclic antidepressants are iminodibenzyl derivatives which resemble phenothiazines in their chemical structure. They are referred to as tricyclic, because their nucleus is

Usual Doses of Antidepressant Drugs in mg.

MAO Inhibitors

Isocarboxazide (Marplan):	20 - 30
Nialamide (Niamide):	100 - 200
Phenelzine (Nardil):	45 - 75
Tranylcypromine (Parnate):	20 - 30

Tricyclics

Imipramine (Tofranil):	50 - 300
Amitriptyline (Elavil):	50 - 300
Desipramine (Norpramin: Pertofrane):	50 - 300
Nortriptyline (Aventyl):	30 - 200
Protriptyline (Vivactil: Triptil):	10 - 80
Doxepin (Sinequan):	50 - 250

Lithium

For maintenance treatment aimed at preventing depressive or manic episodes:	Serum level between 0.6 and 1.1 meq /l.
For treatment of acute manic syndrome:	Serum level between 1.0 and 1.4 meq /l.

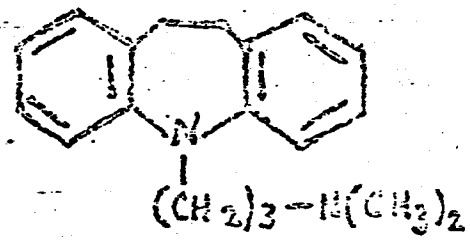
(See Fig.3)
represented by three benzol rings./ Other widely used drugs of the same type are amitriptyline (Elavil) which produces more sedation and drowsiness than imipramine, and the demethylated derivatives of imipramine: desipramine (Pertofrane; Norpramin), and of amitriptyline: nortriptyline (Aventyl). The last named drugs produce less sedation and, as some reports indicate, also fewer other side-effects; however, they may be slightly less effective in their specific antidepressant action. (Hollister et al, 1963; Lehmann, 1965).

There has been a neck-to-neck race between the antidepressant efficacy of imipramine (Tofranil) and amitriptyline (Elavil) for some years. One recent review reports that amitriptyline (Elavil) was superior to imipramine (Tofranil) in four of seven comparative and inferior to it only once. (Morris and Beck, 1974). Another review states that of six such studies amitriptyline (Elavil) was found to be superior to imipramine in two and inferior to it in one study. (Ban, 1974). Furthermore, a follow-up of the most extensive study that had shown the superiority of amitriptyline (Elavil) over a six-month period revealed that twelve months after the study had been completed, there were more relapses among patients on amitriptyline (Elavil) than among those on imipramine (Tofranil). (Kessell and Holt, 1965).

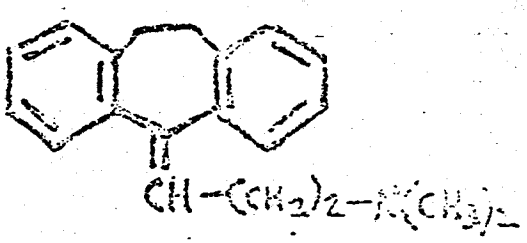
Another tricyclic antidepressant whose chemical structure is somewhat different, because of changes in its side chain, is protriptyline (Vivactil, Triptil). The latest compound to join the family of tricyclic antidepressants is doxepin (Sinequan) which, like amitriptyline, has a primary anxiolytic-sedative effect in addition to its antidepressant action and, unlike most other tricyclics, is claimed not to interact with antihypertension drugs (Castrogiovanni et al, 1971; Whiting et al, 1973) and to produce fewer cardiotoxic effects, if given in therapeutic doses.

Fig. 3

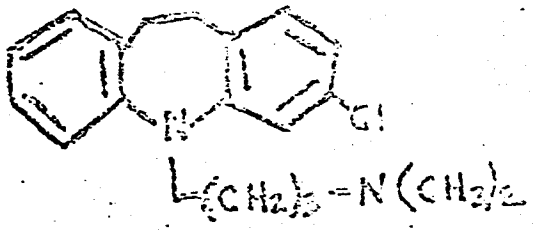
TRICYLIC ANTIDEPRESSANTS



IMIPRAMINE



AMITRIPTYLINE



CHLORIMIPRAMINE

Daily doses of tricyclic antidepressants, marketed in the U.S., are listed on Table II.

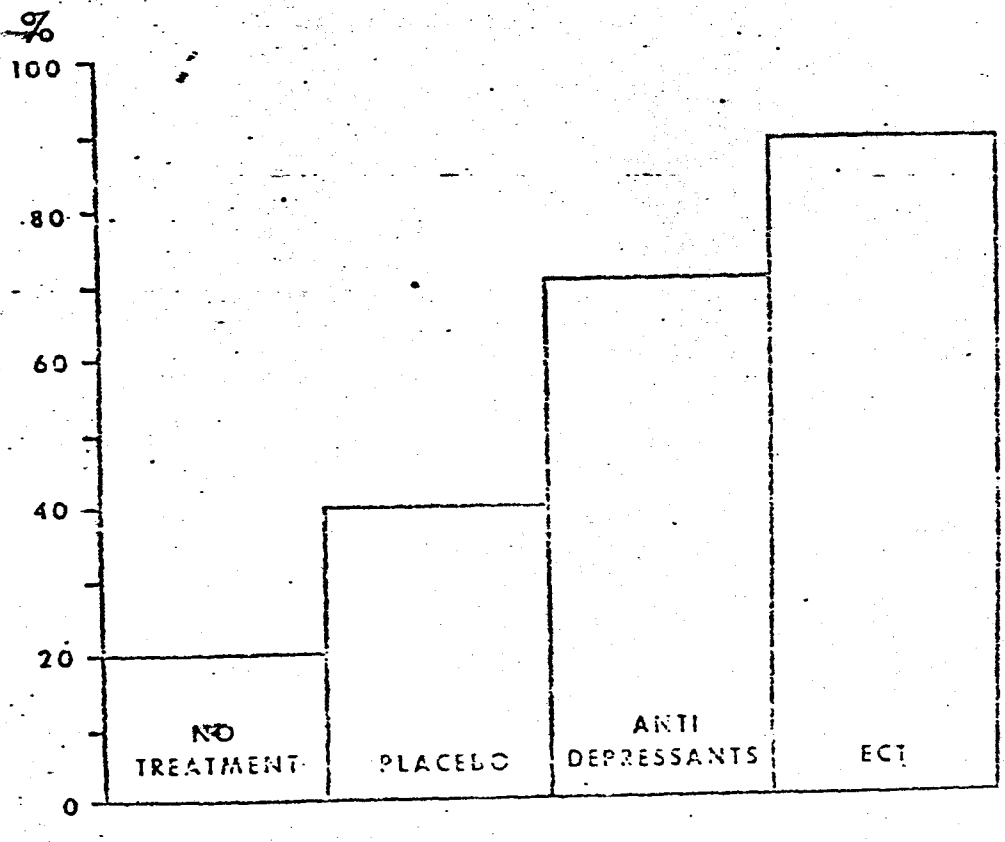
Clomipramine (Anafranil), a tricyclic, and maprotiline (Ludiomil) - a compound with four rings (tetracyclic)-and viloxazine hydrochloride (Vivalan), a new antidepressant compound that differs from the tricyclics in chemical structure and side-effects, are three other antidepressants for which many pharmacological and clinical data are now available. Most of the work with these compounds has been done in Europe, and the drugs are not yet marketed in the U.S. (Anafranil Symposium, 1973; Balestrieri et al, 1971; Editorial J.A.M.A., 1972; Murphy, 1975).

Efficacy of Antidepressant Pharmacotherapy

Hundreds of published reports on antidepressant pharmacotherapy have established the fact that tricyclic antidepressants are definitely - and MAOI's almost certainly - more effective than placebo. It has been pointed out that negative results with MAOI,s in controlled studies might have been due to the administration of inadequate doses. Direct comparisons of the many reported results is extremely difficult because of the great disparity in the type of patients admitted to the different studies. All efforts to reliably isolate homogeneous subgroups of depressed patients have so far proved unsuccessful.

Nevertheless, most results converge toward 60-70 percent efficacy of MAOI's or tricyclic drugs in the treatment of unselected depressions (Klerman and Cole, 1965; Lehmann, 1966). It is instructive to view these results within the perspective of the whole range of possible physical interventions in depressive illness. Figure 4 represents the probability of favourable therapeutic outcomes with various methods of treatment, as well as with placebo or without any specific treatment.

Fig. 4



Legend to Fig. 4

Effectiveness of different treatment modalities in depressed patients. (Percent of patients much improved after three weeks).

It is probably justified at this time to conclude that significant spontaneous improvement of depression within a month occurs in about 20 percent of patients (Burt et al, 1962). Placebos may increase the depressed patient's chances of improvement by another 20-30 percent (Lehmann, 1966; Raskin, 1971). Effective antidepressant drugs which are available today give the patient an additional 20-30 percent chance of improvement. Finally, electroconvulsive treatment (ECT) may be counted on to produce reliable improvement in another 10-15 percent of those patients who have resisted all other treatments.

However, even if the actual therapeutic contribution of antidepressive pharmacotherapy is only from 20-30 percent over and above spontaneous recovery or placebo effects, this is nevertheless an important therapeutic gain, and every attempt to exploit it should be made by the clinician. ECT - even though it has been shown to be the most effective antidepressive therapy (Greenblatt et al, 1962; Brit. Med. Research Council, 1965) - is more difficult to administer than drugs, causes special, disturbing side-effects, and does not lend itself easily to maintenance treatment.

Mechanisms of Action

Two major hypotheses about the somatic substrate of psychiatric depressions are competing at present: one explains depression as the result of deficient catecholamines - more specifically, norepinephrine - at crucial receptor sites in the brain; the other assumes that a deficiency of indoleamines - more specifically, serotonin - at brain receptors is responsible for the manifestations of depression. Both hypotheses can be brought under a common denominator by theorizing that depression is the result of a disturbed ratio and/or quantity of biogenic amines in the CNS, as Prange's group is doing, for example, with their permissive theory of affective disorders. (Prange et al, 1974).

Monoamine inhibitors increase the available amounts of biogenic amines in the CNS by interfering with their metabolic degradation, while tricyclic antidepressants achieve the required increase of biogenic amines by inhibiting the re-uptake of these substances from the synaptic cleft into the neuron. Both classes of antidepressant drugs, thus, counteract a reduction of either catecholamines or indoleamines in the CNS. Experimental work has shown that the rewarding (response-excitatory) effect of electrical stimulation of the medial forebrain bundle depends on the activation of adrenergic synapses in the lateral hypothalamus and that this activation may also be brought about by the action of amphetamine and, probably, norepinephrine. Thus, an increase of catecholamines at these sites in the brain would correct any deficient adrenergic transmission at the synapse - a condition which may serve as a neuro-physiological model of antidepressant therapy. (Stein, 1966).

It has been reported that the secondary amines, e.g., desipramine and protriptyline, inhibit more selectively the uptake of noradrenaline, and the tertiary amines, e.g., imipramine and amitriptyline, the uptake of serotonin. (Modigh, 1973). An interesting parallel appears in the clinical observation that the secondary amines, which affect mainly the noradrenergic neurons, are producing more pronounced motor activation and increased drive, while the tertiary amines, which act predominantly on serotonin-sensitive neurons, are more effective in improving the mood of depressed patients. (Kielholz, 1968).

Side-Effects and Drug Interactions

The interactions of MAOI's with other drugs and various food substances have already been discussed. The most disturbing side-effect of MAOI's is orthostatic hypotension. Other side effects which are not uncommon are weight gain and effects on the CNS, e.g., restlessness and insomnia, impairment of sexual functioning in the form of delayed ejaculation and orgasm, loss of erection and reduced libido.

The most important side-effect of the tricyclics is their potential cardiotoxic action (Moir et al, 1972), which is probably of clinical importance only in pre-existing cardiovascular disorder; but the presence of the latter may not always be known. Arrhythmias and a widening of the QRS complex in the ECG are the manifestations of this cardiotoxic effect, which is always reversible when the drug is discontinued. In elderly patients and in those with known cardiovascular disease, a pre-treatment ECG and subsequent ECG monitoring may be indicated.

Other side-effects of tricyclic antidepressants are: drowsiness, particularly during the first week of administration, dryness of mouth, tremor, sweating, dizziness, constipation, difficulty with voiding, hypotension, delayed ejaculation, headache and - particularly in the elderly - confusional states. None of these symptoms are, as a rule, important enough to interfere seriously with the administration of the antidepressant, except for severely neurotic patients who seem to be specially sensitive to side-effects, and for alcoholics who find it impossible to take adequate doses of tricyclic antidepressants, if they continue to drink heavily at the same time.

Because all tricyclic antidepressants have anti-cholinergic properties, caution is indicated when prescribing these drugs for patients suffering from untreated closed angle glaucoma (Drug Therapy Bulletin, 1975) or symptoms of disturbed micturition. For the same reason, it is unwise to prescribe tricyclic antidepressants in a triple combination with a neuroleptic drug, e.g., a phenothiazine, and an antiparkinson drug, since most neuroleptics - and practically all anti-parkinson drugs - have anticholinergic properties of their own, which have an additive or potentiating effect on the anticholinergic activity of the tricyclic antidepressant and may produce dangerous, even fatal complications, e.g., adynamic ileus (Warnes et al, 1967). The combination of a tricyclic anti-

depressant with a neuroleptic (major tranquilizer) alone is usually well tolerated, as long as no antiparkinson drug is added to it. Tricyclic antidepressants may also be administered together with most anxiolytic sedatives (minor tranquilizers), except barbiturates, without adverse effects, although confusional states have occasionally been observed following the simultaneous administration of tricyclics with benzodiazepines (Martin, 1971). Some of the interactions of antidepressant drugs with other drugs are listed on Table III and relative contra-indications to the different treatment modalities in depression on Table IV.)

Barbiturates - probably by means of enzyme induction - lower the plasma level of tricyclic antidepressants and thus their therapeutic efficacy. (Nakazawa, 1970; Sjöqvist et al, 1968). Methylphenidate (Ritalin), on the other hand, inhibits the metabolism of imipramine and causes an increase in serum levels of imipramine and desipramine; this may have a potentiating effect on the therapeutic action of these antidepressants. A similar interaction has been observed with some phenothiazines, also resulting in an increase of tricyclic plasma levels. (Perel et al, 1969; Garrettson et al, 1969; Wharton et al, 1971; Rafaelsen and Gram, 1974). Inhibition of the metabolism of imipramine, has also been observed when high doses of oestrogen are taken (Prange, 1974; Khurana, 1972). Furthermore, an antagonism has been observed between the hypotensive action of guanethidine and imipramine, possibly because the tricyclics compete successfully with guanethidine, bethanidine and bretyllium for the adrenergic receptor sites and thus prevent their full hypotensive action. An interaction with methyldopa (Aldomet) has not been definitely demonstrated but is suspected. (Leishmann et al, 1963; Mitchell et al, 1970; Stockley, 1972).

Sleep studies have shown that imipramine, desipramine, amytriptyline and doxepin produce an immediate reduction of REM sleep. Some tricyclic antidepressants increase intrasleep

Tricyclic Antidepressants:

Interactions with other Drugs (Several not definitely established)

Interacting Drugs	Probable Effects
Barbiturates	Reduced Plasma Level
Methylphenidate	Increased Plasma Level
Thyroid (Tri-iodothyronine)	Enhanced Antidepressant Effect in female patients
MAO Inhibitors	Enhanced Antidepressant Effect and Toxicity
Guanethidine	Decreased Hypotensive Effect
Phenothiazines	Enhanced Sedation and Increased Plasma Level
Anticholinergics	Enhanced Side Effects
Physostigmine	Reduction of Anticholinergic Effects
Minor Tranquilizers	Enhanced Sedation
Alcohol	Enhanced Sedation
Cigarettes	Reduced Plasma Level
Estrogens (oral contraceptives?)	Increased Plasma Level
Reserpine	Enhanced Antidepressant Effects (and Toxicity)

Relative Contraindications to Different Treatment Modalities in Depression

ECT	Age over 60. (Persistent memory defect) Organic Brain Lesion. Decompensated Circulatory Disease. Fever. States of high anxiety.
Tricyclic Antidepressants	Glaucoma, particularly of the untreated closed angle type. Prostatic Hypertrophy. Myocardial Disease. Cardiac Arrhythmias. Age over 60 (Monitor E.C.G. For cardiac toxicity)
MAO-Inhibitors	Hypotension. Alcoholism. Low Intelligence. Low Reliability. Patients on thyroid, adrenergic or tricyclic antidepressant drugs
Lithium	Age over 60. (Unstable renal clearance; difficult control of serum level; lower threshold of toxicity Hypothyroidism. Kidney, Liver, Circulatory Disease. Patients on Diuretics.

restlessness, e.g. imipramine and desipramine, while others seem to decrease restlessness during sleep, e.g. doxepin. (Fram et al, 1970; Duleavy et al, 1972).

Finally, lithium, which is frequently used in the maintenance treatment of recurrent depressions, interacts with most diuretics to the effect that its clearance is impaired, and its serum level increased; under these conditions there is a greater risk of toxicity.

Methodological Problems

The pathophysiology of depression has not yet been definitively established. One is tempted to accept the existing theory involving a disturbed balance of biogenic amines in the brain, but because it is based on circumstantial evidence only, the theory lacks experimental proof and furnishes us with little detail.

Since there is as yet no real animal model for emotional depression, pharmacologists have circumvented the problem by adopting certain pharmacologically or physiologically produced experimental states animals as some approximation to, or models of, depression, e.g. the reserpine-induced state of altered behaviour and metabolism. In a provocative review of the existing data, McKinney and Bunney (1969) have proposed research strategies which could be used to create animal models of depression which etiologically and phenomenologically represent better approximations to depressive disorders in humans.

Another problem arises from the fact that it is impossible to know what proportion of metabolites of catechol - or indoleamines measured in various body fluids, e.g. urine, blood or cerebro-spinal fluid, reflects processes in the CNS, and how much it results from peripheral processes.

Still another unsolved problem faces the clinical investigator whose controlled clinical trials with antidepressant drugs require homogeneous groups of depressed patients. Until now, no clear criteria are known that would enable a researcher to screen depressed patients, in order to form such homogeneous samples. However, much experimental, genetic, epidemiological and statistical work is going on in this area, and there is reason to hope that the identification of homogeneous groups of depressed patinets will be achieved with greater precision in the not too distant future.

Predictors of Treatment Outcome and Choice of Drugs

Unlike ECT, pharmacotherapy of depression, even if effective, does not produce dramatic improvement within a few days. As a rule, it takes from one to three weeks before it becomes evident whether or not a patient is responding to treatment. Because of this long waiting period, it would be helpful if there were methods to predict the patient's eventual response to chemotherapy and the specific drugs, before embarking upon the treatment. No generally applicable predictors of this kind exist today.

However, there are methods of predicting therapeutic outcome which are effective in certain special situations. Applying pharmacogenetic principles, Pare et al (1962) and Angst (1964) have observed that a depressed patient will often respond to the same antidepressant treatment that has been effective in other members of his family. For instance, if a relative of a depressed patient has previously responded well to a MAOI, the patient himself is likely to improve with the same type of treatment. Similarly, therapeutic responsiveness to tricyclic antidepressants also seems to run in families.

The probenicid test is a procedure which prevents the excretion of biogenic amines and metabolites from the CNS,

so that their accumulation in the cerebro-spinal fluid may be measured. (Goodwin and Gordon, 1973). Van Praag and his coworkers (1972) have reasoned that those depressed patients in whom it could be demonstrated that serotonin metabolism was specifically disturbed, would show a therapeutic response to treatment with the serotonin precursor 5-hydroxytryptophan. Having selected those patients in whom the probenicid test revealed a relative decrease of serotonin turnover, they reported encouraging results of this type of biochemically selected treatment in depressed patients who had previously been therapy-resistant.

A biochemical predictor of therapeutic response in depressed patients whose catecholamine metabolism is specifically affected, may be 3-methoxy - 4-hydroxyphenylglycol (MHPG) which has been claimed to reflect more central than peripheral catecholamine turnover. Schildkraut (1973) reported tentative findings, that imipramine seems to be most effective in the depressed patients whose MHPG excretion is lowest, and that amitriptyline seems to produce the best therapeutic response in depressed patients with relatively higher levels of MHPG.

An interesting predictor for phenelzine-responsive depressed patients has been studied by Johnstone and Marsh (1973). These investigators measured the genetically determined speed of metabolic acetylation in depressed out-patients and related it to the therapeutic response to phenelzine. The results suggested that phenelzine was effective for slow acetylators. The variable results that have been observed with phenelzine may be explained by the fact that this drug may be only indicated in depressed patients who are slow acetylators.

The possibility of using measurements of the monoamine oxidase content of blood platelets as indicators and predictors of the efficacy of antidepressant therapy has also been discussed. (Robinson et al, 1974).

Attempts to relate the plasma level of tricyclic antidepressants directly to the clinical response have so far been unsuccessful. Burrows et al (1972) found that in patients receiving 150 mg. nortriptyline per day, there was considerable inter-individual variability of plasma levels, but no prediction of the therapeutic response could be made on the basis of these differences. Others have shown that side-effects may be related to the plasma level of a tricyclic drug and that best clinical results are observed in a middle range of plasma levels which may be related, in non-linear fashion, to tricyclic plasma levels. (Sjöqvist et al, 1968; Asberg et al, 1974; Braithwaite et al, 1972; Kragh - Sörensen et al, 1973).

Wittenborn (1967) has studied possible correlations of premorbid personality factors with antidepressant treatment outcome and observed that depressed patients with a history of manic-depressive illness, involutional melancholia or paranoid personality features reacted poorly, while the reactive diagnostic group responded favourably to imipramine. This is in contrast to most other published findings which report a better therapeutic response of endogenous depressions to tricyclic antidepressants. (Klerman and Cole, 1965; Raskin, 1971).

Exploring the influence of socio-economic factors on the therapeutic response of depressed patients to amitriptyline and chlordiazepoxide (Librium), alone and in combination, Rickels et al (1970) observed that in the treatment of mildly to moderately depressed outpatients the type of drug is of much less importance in patients belonging to the lower socio-economic classes than in the middle social class patients, who also responded less frequently to placebo than the lower class patients.

Perhaps the most reliable predictors of therapeutic responses to antidepressant drugs are still the clinical symptoms. It has already been mentioned that some clinicians feel MAOI's are more specifically indicated in neurotic depressions with hysterical and anxiety symptoms. Nevertheless, a recent controlled comparative study established that the tricyclic amitriplyline, given to depressed outpatients, produced not only somewhat faster relief from their depressive symptoms than the MAOI phenelzine, but also greater improvement in the neurotic features (Kay et al, 1973). For the treatment of episodic panic attacks, Klein (1964) found imipramine and MAOI's equally effective.

Hollister and Overall (1965) reported that imipramine was particularly effective in the treatment of retarded depressions, while hostile and anxious depressions responded better to the neuroleptic thioridazine (Mellaril). However, a recent study with imipramine in neurotic, depressed patients proved the effectiveness of this tricyclic in the anxious as well as the retarded patients. (Covi et al, 1974). A fairly consistent finding in various studies was a tendency for female depressed patients to show a poor response to imipramine if they had a history of suicide attempt or paranoid features. (Kiloh et al, 1962; Robin and Langley, 1964; Wittenborn, 1966).

Finally, in two controlled comparative studies on the effects of various psychotropic drugs on depressed patients, it was observed that imipramine, chlorpromazine (Thorazine) and diazepam (Valium) were equally effective for sleep disturbances, imipramine was best for depressive and anergic symptoms and diazepam was most suited for the treatment of anxiety symptoms. (Raskin, 1971).

Maintenance Treatment

Until recently the prophylactic maintenance treatment of patients suffering from recurring depressions was much less reliable than that of schizophrenic patients. Relatively few controlled studies of this problem are available. Imlah et al (1964) could show that patients who had recovered from a depressive episode and were maintained on imipramine, had a significantly lower relapse rate in the following six months than patients who were given placebo. In a recent double-blind, controlled study, Midham et al (1972) could show that the relapse rate of patients who had recovered from a depressive episode and were continued on tricyclic antidepressants, at lower than treatment doses, for the following six months, had a relapse rate of 22 percent, while patients continued on placebo had a 50 percent incidence of relapse.

A controlled, large-scale study, undertaken by the U.S. Veteran's Administration (Prien et al, 1973), has recently demonstrated convincingly that the maintenance of depressed patients - that is, prevention of recurring depressive episodes - is equally effective with imipramine or lithium carbonate in unipolar depressions, but is significantly more effective with lithium than with imipramine in bipolar depressions. This finding allows the clinician a rational choice of the chemical agent he wants to administer to patients with recurrent depressions, if he has decided to keep the patient on continued pharmacotherapy for some time, once he has recovered from his depressive episode. In most cases, this is a wise precaution to adopt. (Lehmann, 1965).

How long such maintenance treatment should be continued is a question which at this time only clinical judgment can decide. Lithium maintenance treatment often does not become fully effective for a year, and once it has been embarked upon it should not be given up - except for severe side effects or toxicity - before at least one year has elapsed. In some cases maintenance treatment must be continued for several years, sometimes for the lifetime of the patient.

Whether, for a patient suffering from unipolar depressions, one should choose a tricyclic, e.g. imipramine or lithium as the maintenance drug would depend on several considerations. How well does the patient tolerate imipramine or lithium? Can he be trusted to come regularly for the periodic determinations of lithium plasma levels? How long are the phases when the patient is well? Has he had more than one affective episode during the last three years? Answers to all these questions enter into the making of the final clinical decision.

Since the significance of apparent interactions of lithium with the plasma levels of tricyclic antidepressants has not yet been clarified, it would, at the present time, seem advisable to interrupt any lithium maintenance treatment for the duration of an acute depressive episode that may require tricyclic antidepressant therapy.

Other Treatments

Although it is known that the combination of MAOI's with tricyclic antidepressants may result in dangerous hypertensive reactions, states of hyperpyrexia, agitation, confusion, convulsion, coma and death (Bowen, 1964; Lockett and Milner, 1965; Beaumont, 1973), some clinicians - particularly in Britain - recommend this combined chemotherapy as being often successful in depressed patients who have failed to respond to all other available treatments. (Gander, 1967; Pare, 1968). Apparently, complications of such combined treatment can be minimized if the doses of the MAOI and tricyclic antidepressant are built up very slowly and simultaneously over a period of two to three weeks (Pare, 1968), and if amitriptyline is chosen as the tricyclic drug, because it is a weaker potentiator of noradrenaline than imipramine. (Sethna, 1974).

The addition of the thyroid hormone triiodothyronine to imipramine enhances the therapeutic action of imipramine in depressed patients, as Prange et al (1970) first reported. The authors explained this by postulating an interaction of triiodothyronine and imipramine to produce an elevation of adrenergic activity, a hypothesis which later could be experimentally confirmed. (Breese et al, 1972).

The intravenous instead of the traditional oral route of administration of tricyclic antidepressants has been employed by some clinicians. The drug most frequently chosen for intravenous infusion is clomipramine*, and this kind of therapy has been claimed to be effective not only in depressions but also for the relief of obsessive-compulsive and phobic symptomatology (Cordoba and Lopez Ibor, 1967; Capstick, 1970; Marshall and Micev, 1973; Rack, 1973). However, because side-effects and complications may be more frequent with this kind

*available in Canada, but not yet in the U.S.

of administration, Rigby et al (1973) suggest that the use of the intravenous route be reserved for those who have failed to respond to oral medication.

Because it is currently assumed that intracerebral catecholamines play a significant role in the etiology of depressive conditions, treatment of depressed patients with L-Dopa, alone or in combination with other antidepressants, has been tried by a number of investigators with varying success. (Klerman et al, 1963; Fracasso et al, 1972). Bunney et al (1972) reported that the use of L-Dopa as an antidepressant was clearly ineffective in most of their patients, and that the drug almost regularly evoked manic symptoms in those patients who suffered from a bipolar depression.

Tryptophan, a precursor of serotonin, has been introduced as an antidepressant by those investigators who consider a deficient serotonin turnover as the principal etiological factor of the depressive state. (Coppen et al, 1967; Sano I, 1972). L -Tryptophan, by itself and in combination with an MAOI antidepressant, has been reported to give good clinical results (Ayuso Gutierrez and Lopez Ibor Alino, 1971). A dose of 9 mg L-Tryptophan per day proved to be as effective as 150 mg of imipramine per day in its antidepressant action. The addition of triiodothyronine enhanced the antidepressant action of imipramine, but not that of tryptophan. (Coppen et al, 1972).

Thyrotropin Releasing Hormone (TRH) is one of the latest antidepressant agents. Prange and Wilson (1972) had observed that TRH will potentiate L-Dopa-induced behavioral activation in mice and then tested the hormone for possible antidepressant activity. They found that single doses of

TRH, given intravenously, produced a distinct improvement of depressive symptoms. Onset of this improvement was observed after two hours, and the antidepressant effect lasted from six to thirty hours. A replication of the clinical trial with TRH confirmed the earlier observations. (Kastin et al, 1972). The antidepressant action of TRH is probably not mediated through the pituitary, but seems to be a central effect, since potentiation of L-Dopa-induced activation of behavior by TRH occurs also in hypophysectomized animals. (Prange et al, 1972). Whether or not this interesting observation will acquire clinical significance and eventually produce more lasting improvement, only the future will show. Several studies conducted in Europe have thrown doubt on the antidepressant effectiveness of TRH. (Benkert et al, 1974).

A therapeutic approach to the treatment of depression, which differs in several aspects from most other antidepressant chemotherapies, has been tried by Lehmann et al (1971). They treated a group of depressed patients - including some geropsychiatric patients - with injections of 50 mg. of meperidine (Demerol) and the simultaneous oral administration of 10 mg of dextro-amphetamine (Dexedrine) on alternate days, repeated five times. Their results, as measured by clinical findings and ratings on the Hamilton Depression Rating Scale, were encouraging: in most cases considerable improvement occurred and was maintained for long periods. The mechanism of action of this therapy may be partly based on shifts in the central turnover of biogenic amines, e.g. a meperidine-induced increase of noradrenaline, and partly on a reconditioning of affective and mood-related processes occurring after the repeated experience of pharmacologically-induced states of well-being. However, these findings have not been confirmed by others or by double-blind controlled observations.

Lithium, which has proved so successful in the treatment of manic episodes and in the prevention of relapses of manic or depressive episodes in patients with bipolar affective disorders, has also been tried in the treatment of depressive episodes. Although good results in the treatment of both unipolar and bipolar depressions have been reported by some (Rybakowski, 1972), others have observed favourable therapeutic results mainly with bipolar depressions. Himmelhoch et al (1972) were successful with the combination of lithium and an MAOI in a group of 9 bipolar depressed patients who had resisted previous treatment with tricyclics, and Goodwin et al (1972) observed some improvement with lithium - as the only antidepressant - in 80 percent of bipolar, but in only 33 percent of unipolar depressions.

Table V gives an overview of the effectiveness of various established and experimental antidepressants on different dimensions of psychopathology.

Treatment-Resistant Depressions

Every clinician has probably had the bad fortune to encounter depressed patients who did not improve, in spite of all his efforts. Although, in general, depression is a disease with a good prognosis, and most depressions would eventually terminate by self-recovery, there are certain depressive syndromes where all therapeutic efforts are doomed to failure. One or more of the following eight factors are usually involved in these cases:

1. inappropriate mode of treatment, inappropriate drug or inadequate dosage and duration of therapy;
2. association of the depression with organic brain damage or alcoholism;
3. ongoing life situations and existential contingencies which are inevitable and intolerable, e.g. severe, permanent disability, advanced age and loneliness;

Table V

Effectiveness of Established and Experimental Antidepressants on Different Dimensions of Psychopathology

	Depressive Symptoms	Anxiety Symptoms	Psychotic Symptoms
Antidepressants (Tricyclics or MAOI's)	++	+	-
Anxiolytics	+	++	0
Neuroleptics	(+)	+	++
Amphetamine-like drugs	(+)	-	-
Lithium	(+)	(+)	0
L-dopa	(+)	0	(-)
Tryptophane	(+)	0	(-)(+)
Peptides, e.g. TRH: MIF, etc.	(+)	0	(+)

++ or +: effective
(+): sometimes effective
0 : ineffective
-: antitherapeutic
(-): sometimes antitherapeutic

4. a life history with uniquely traumatizing situations, e.g. concentration camp experiences;
5. a lifelong depressive character structure with a specific, antitherapeutic psychodynamic constellation;
6. hypochondriasis or schizophrenic admixture;
7. over 45 years of age;
8. duration of depression longer than 1 year.

Fortunately, the first factor, i.e. inappropriate or inadequate treatment, accounts for most cases of treatment-resistant depressions; it is also the factor that can most easily be changed in the patient's favour. The other factors are difficult or sometimes impossible to modify. However, psychotherapy, continued interest, support, and encouragement on the part of the psychiatrist, combined with his sustained medical efforts to provide at least some measure of relief for the patient, can in some of these patients improve their prognosis.

SUMMARY AND CONCLUSIONS

Chemotherapy of depression is today well established as the first treatment of choice for all pathological, persistent, depressive states. Sleep deprivation is an easily administered treatment that, in endogenous depressions, may enhance the effects of antidepressant drugs. Whenever the state of depression is extremely acute and life-threatening, because of unmanageable agitation or suicidal impulses, or when chemotherapy has proved unsuccessful for more than 4 weeks, ECT is indicated. Psychosurgery may, in refractory cases, be considered as a last resort. Psychotherapy is often required - particularly in reactive depressions after the acute symptoms have subsided.

There are two principal types of antidepressant drugs: The MAOI's and the tricyclics. The choice of the particular drug to be used is today still best determined by clinical symptoms, but may soon be based on biochemical factors.

Maintenance treatment of patients after the termination of their depressive episode is recommended, at least for some months, but often for years. In patients who have suffered from a bipolar depression, lithium is the most effective maintenance treatment; in unipolar patients, imipramine is equally effective.

Active research into the physio-chemical substrate of depression is rapidly progressing, and although the ideal antidepressant has not yet been found, many original, provocative and promising leads are being offered to the perceptive and knowledgeable clinician.

References

Alexander, L. and Berkeley, A.W.: The inert psychasthenic reaction (anhedonia) as differentiated from classic depression and its response to iproniazid. Am. N.Y. Acad. Sci., 80, 669, 1959.

Anafranil Symposium: Murphy, J., editor. The Journal of International Medical Research, 1/5: 271-488, 1973.

Angst, J.: Antidepressiver Effekt und genetische Faktoren. Arzneimittel-Forsch, 14: 496, 1964.

Asberg, M., Kragh-Sørensen, P., Bertilsson, L., Cronholm, B., Eggert-Hansen, Ch., Sjöqvist, F., Tuck, J.R.: Studies of relationship between plasma level and clinical effects of Nortriptyline - Methodological problems, in Symposia Medica Hoechst (8), editors: Classification and Prediction of Outcome of Depression, F.K. Schattauer Verlag GmbH., Stuttgart, Germany, 1974, 181-192.

Ayuso Gutierrez, J.L., and Lopez Ibor Aliño, J.J.: Tryptophan and an MAOI (nialamide) in the treatment of depression. A double blind study, Int. Pharmacopsychiat. (Basel), 6/2: 92-97, 1971.

Balestrieri, A., Benassi, G.B., Castrogiovanni, P., Catalano, A., Colombi, A., Conforto, C., Del Soldata, G., Gilberti, F., and Sarteschi, P.: Clinical comparative evaluation of maprotiline, a new antidepressant drug, Int. Pharmacopsychiat. 6: 236-248, 1971.

Ban, T.A.: Depression and the Tricyclic Antidepressants, Ronalds Federated Graphics Limited, Montreal, 1974.

Beaumont, G.: Drug interactions with clomipramine (Anafranil), J. Int. Med. Res. 1: 480-484, 1973.

Bhanji, S., and Roy, G.A.: The treatment of psychotic depression by sleep deprivation: A replication study, Brit. J. Psychiat., 127: 222-226, 1975.

Bowen, L.W.: Fatal hyperpyrexia with antidepressant drugs, Brit. Med. J., 2: 1465, 1964.

Braithwaite, R.A., Goulding, R., Theano, Ginette, Baily, J., and Copper A.: Plasma concentration of amitriptyline and clinical response, Lancet, 1: 1297-1300, June 17, 1972.

Breese, G.R., Traylor, T.D., and Prange, Jr., A.J.: The effect of triiodothyronine on the disposition and actions of imipramine, Psychopharmacologia (Berl.), 25/2: 101-111, 1972.

Brit. Med. J. 1: 881, 1965: Clinical trial of the treatment of depressive illness. Report to the Medical Research Council by its Clinical Psychiatry Committee.

Bunney, Jr., W.E., Gershon, E.S., Murphy, D.L. and Goodwin, F.K.: Psychobiological and pharmacological studies of manic depressive illness, J. Psychiat, Res. 9/3: 207-226, 1972.

Burrows, G.D., Davies, B., Scoggins, B.A.: Plasma concentration of nortriptyline and clinical response in depressive illness, Lancet, 2: 619-623, 1972.

Capstick, N.: Chlorimipramine (Anafranil) in the treatment of obsessional states. Paper read at the 7th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Prague, 1970.

*Benkert, O., Hartschek, I. and Gordon, A.: Comparison of T.R.H., L.H.-R.H., and placebo in depression, Lancet, 2: 1146, November 1974.

Castrogiovanni, P., Placidi, G.F., Maggini, C., Ghetti, B., and Cassano, G.B.: Clinical investigation of doxepin in depressed patients. Pilot open study, controlled double-blind trial versus imipramine and all-night polygraphic study, Pharmacopsychiatric Neuropsychopharmacologie 4: 170-181, 1971.

Cole, M.G., and Müller, H.F.: The treatment of endogenous depression by 36-hour sleep deprivation. Paper presented at the Canadian Psychiatry Association Annual Meeting in Banff, Alberta, September 1975.

Coppen, A., Shaw, D.M., Herzberg, B. and Maggs, R.: Tryptophan in the treatment of depression, Lancet, 1178-1180, December 2, 1967.

Coppen, A., Whybrow, P.C., Noguera, R., Maggs, R. and Prange, Jr., A.J.: The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine, Arch. Gen. Psychiat., 26: 234-240, March 1972.

Cordoba, F.E., and Lopez-Ibor, J.J.: Monochlorimipramine in psychiatric patients resistant to other forms of treatment, Acta Luso-Espanolas de Neurologia y Psiquiatrica 26: 119, 1967.

Covi, L., Lipman, R., Derogatis, L.R., Smith, J.E. and Pattison, J.H.: Drugs and group psychotherapy in neurotic depression, Am. J. Psychiat. 13: February 2, 1974.

Cox, J.M.: Practical Observations on Insanity, London, 1804.

Crisp, A.H., Hays, P. and Carter, A.: Three amine oxidase inhibitor drugs in the treatment of depression, Lancet, 1: 17, 1961.

Diepz, J.: ECT study reveals disparity between public, private units, Psychiatric News 10/5: 1, August 6, 1975.

Drug. Ther. Bull. 13/2: 7-8, 1975: Tricyclic antidepressives and glaucoma: What's the risk?

Dunleavy, D.L.F., Brezinova, V., Oswald, I., Maclean, A.W. and Tinker, M.: Changes during weeks in effects of tricyclic drugs on the human sleeping brain, Brit. J. Psychiat., 120: 663-672, June, 1972.

Editorial: New drug shows promise in depressive patients, J. Am. Med. Association, 220/5: 661-662, 1972.

Fracasso, G.L., Frisone, L. and Parmigiani, P.: Clinical effect of combined administration of levodopa and tricyclic antidepressive agents in the treatment of depressive syndromes, Rass. Studi Psychiat. 61/2: 176-185, 1972.

Fram, D.H., Wyatt, R.J., and Snyder, F.: Longitudinal sleep patterns in depressed patients treated with amitriptyline, Psychophysiology 7/2: 317, 1970.

Gander, D.R.: The clinical value of monoamine oxidase inhibitors and tricyclic antidepressants in combination, in: Garattini, S., and Dukes, M.N.G., editors; Antidepressant Drugs, Excerpta Medica Foundation, 1967.

Garrettson, L.K., Perel, J.M. and Dayton, P.G.: Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate, J. Am. Med. Ass., 207/11: 2053-2056, 1969.

Gillis, A. and Salfield, D.J.: Treatment of depressive states with dinitrile succinate, J. Ment. Sc. 99: 542-546, July, 1953.

Goodwin, F.K., and Gordon, E.K.: Cerebrospinal fluid amine metabolites in affective illness: The probenecid technique, Amer. J. Psychiat., 130/1: 73-79, 1973.

Goodwin, K., Murphy, L., Dunner, L. and Bunney, W.E.: Lithium response in unipolar versus bipolar depression, Amer. J. Psychiat., 129/1: 76-79, July, 1972.

Greenblatt, M., Grosser, G.H. and Wechsler, H.: A comparative study of selected antidepressant medications and EST, Amer. J. Psychiat., 119: 144-153, 1962.

Himmelhoch, J.M., Detre, T., Kupfer, D.J. et al: Treatment of previously intractable depressions with tranylcypromine and lithium, J. Nerv. Ment. Dis., 155/3: 216-220, 1972.

Hollister, L.E., Overall, J.E., Johnson, M., Katz, G., Kimbell, I., and Honigfeld, G.: Evaluation of desipramine in depressive states, J. New Drugs, 3: 166-171, 1963.

Hollister, L.E., and Overall, J.E.: Reflections on the specificity of action of antidepressants, Psychosomatics. 6: 361-365, 1965.

Hurwitz, T.D.: Electroconvulsive therapy: A review, Comprehens. Psychiat. 15/4: 303-314, 1974.

Imlah, N.W., Ryan, E. and Harrington, J.A.: The influence of antidepressant drugs on the response to ECT and subsequent relapse rates. Presented at the Fourth Annual Meeting of the Collegium Internationale Neuropsychopharmacologicum: Birmingham, 1964, 438-442. Excerpta Medica Foundation, Amsterdam.

Johnstone, E.C., and Marsh, W.: Acetylator status and response to phenelzine in depressed patients, Lancet, 1: 567-570, March 17, 1973.

Kastin, A.J., Elwensing, R.H., Schalch, D.S., and Anderson, M.S.: Improvement in mental depression with decreased thyrotropin response after administration of tyrotropin-releasing hormone, Lancet, 2: 740-742, 1972.

Kay, D.W.K., Garside, R.F., Fahy, T.J.: A double-blind trial of phenelzine and amitriptyline in depressed out-patients. A possible differential effect of the drugs on symptoms, Brit. J. Psychiat., 123: 63-67, 1973.

Kessell, A. and Hold, N.F.: Depression - an analysis of follow-up study, Brit. J. Psychiat. 3: 1143-1153, 1965.

Khurana, R.C.: Estrogen imipramine interaction, J. Amer. Med. Ass., 222/6: 702-703, 1972.

Kielholz, P.: Die Behandlung endogener Depressionen mit Psychopharmaka, Deutsche Chirurg. Mediz. Wochenschrift 93: 701, 1968.

Klaesi, J.: Dauernarkose mittels Somnifen bei Schizophrenen: Ztschr. Ges. Neurol. Psychiat., 74: 557-592, 1922.

Klein, D.F.: Delineation of two drug-responsive anxiety syndromes, Psychopharmacologia, 5: 397-403, 1964.

Klein, D.F.: Indications for specific treatments of depressions, Psychopharmacology Bull, 11/3: 3-13, July 1975.

Kiloh, L.G., Ball, J.R.B. and Garside, R.F.: Prognostic factors in treatment of depressive states with imipramine. Brit. Med. J., 1: 1225-1227, 1962.

Klerman, G.L., Schildkraut, J.J., Hasenbush, L.L., Greenblatt, M. and Friend, D.G.: Clinical experience with dihydroxyphenylalanine (Dopa) in depression, J. Psychiat. Res. 1: 289-297, 1963.

Klerman, G.L., and Cole, J.O.: Clinical pharmacology of imipramine and related antidepressant compounds, Pharmacological Reviews, 17/2: 101-141, 1965.

Kline, N.S.: Clinical experience with iproniazid (Marsilid), J. Clin. Exp. Psychopath, 19/2: Suppl.1, 72, 1958.

Kragh-Sorensen, P., Asberg, M. and Eggert-Hansen, C.: Plasma-nortriptyline levels in endogenous depression, Lancet 1, 113, 1973.

Kuhn, R.: Uber die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G 22355). Schw. Med. Wchnschr. 35/36: 1135-1140, Aug. 31, 1957.

Lehmann, H.E.: Problems of differential diagnosis and choice of therapy in depressive states, Psychosomatics, VI; 266-272, Sept.-Oct. 1965.

Lehmann, H.E.: Non-Mao inhibitor antidepressants in clinical perspective. Antidepressant drugs of Non-MAO inhibitor type -- Proceedings of a Workshop. National Institute of Mental Health, U.S., Department of Health, Education and Welfare, Public Health Service, 1966.

Lehmann, H.E., Ananth, J.V., Geagea, K.C., and Ban, T.A.: Treatment of depression with dexedrine and demerol, Current Therapeutic Research 13/1: 42-49, January 1971.

Leishmann, A.W.D., Matthews, H.L. and Smith, A.J.: Antagonism of Guanethidine by imipramine, Lancet, 1: 112, 1963.

Leitch, A. and Seager, C.P.: A trial of four antidepressant drugs, Psychopharmacologia, 4: 72-77, 1963.

Levy, R.: The clinical evaluation of unilateral ECT, Brit. J. Psychiatry, 114: 459-463, 1968.

Livingston, K.E.: Cingulate cortex isolation for the treatment of psychoses and psychoneuroses, Res. Publs. Ass. Res. Nerv., Ment. Dis., 31: 374-378, 1953.

Lockett, M.F., and Milner, G.: Combining the antidepressant drugs, Brit. Med. J., 1: 921, 1965.

Marshall, W.K., and Micev, V.: Clomipramine (Anafranil) in the treatment of obsessional illnesses and phobic anxiety states, J. Int. Med. Res. 1, 403-412, 1973.

Martin, E.W.: Hazards of Medication, J.B. Lippincott, Philadelphia, 1971.

McKinney, Jr., W.T., and Bunney, Jr., W.E.: Animal model of depression - I. Review of evidence: Implications for research. Arch. Gen. Psychiat. 21: 240-248, August, 1969.

Mindham, R.H.S., Howland, C. and Shepherd, M.: Continuation therapy with tricycle antidepressants in depressive illness, Lancet 2/7782: 854-855, 1972.

Mitchell, J.R., Cavanaugh, J.H., Arias, L., and Oates, J.A.: Guanethidine and related agents. III. Antagonism by drugs which inhibit the norepinephrine pump in man, Journal of Clinical Investigation, 39: 1596, 1970.

Modigh, K.: Effects of clomipramine (Anafranil) on neurotransmission in brain monoamine neurones, J. Int. Med. Res. 1, 274-280, 1973.

Moir, D.C., Crooks, J., Sawyer, P., Turnbull, M.J., and Weir, R.D.: Cardiotoxicity of tricyclic antidepressants. Pr. J. Pharmacol. (A): 271, 1971.

Morris, J.B. and Beck, A.T.: The efficacy of antidepressant drugs: A review of research 1958-1972, Arch. Gen. Psychiat. 30: 667-674, 1974.

Murphy, J.E.: Vivalan: Drug profile, J. Int. Med. Res. 3, Suppl. 3/122: 122-124, 1975.

Nakazawa, K.: Studies on the demethylation, hydroxylation and N-oxidation of imipramine in rat liver, Biochem. Pharmacol. 19: 1363-1369, 1970.

Ostrow, D.E., and Lehmann, H.E.: Quizzing the expert: Clinical criteria for psychosurgery, Hospital Physician 2: 24-31, 1973.

Pare, C.M.B., Rees, L., and Sainsbury, M.J.: Differentiation of two genetically specific types of depression by response to antidepressant drugs, Lancet, II, 1340, 1962.

Pare, C.M.B.: Recent advances in the treatment of depression, in Coppen, A. and Walk, A., editors: Recent Developments in Affective Disorders, Headley Brothers Ltd., Ashford, Kent. 1968, 137-150.

Perez, J.M., Black, N., Wharton, R.N., and Ma[illegible] S.: Inhibition of imipramine metabolism by methylphenidate. Federal Proceedings 28: 418, 1969.

Pflug, B.: Über den Schlafentzug in der ambulanten Therapie endogener Depression, Der Nervenarzt, 43: 614-622, 1972.

*

Prange, Jr., A.J., Wilson, I.C., Lipton, M.A., et al: Use of a thyroid hormone to accelerate the action of imipramine, Psychosomatics 11/5: 442-444, 1970.

* Pinel, P.: Ellébore, in: Encyclopédie méthodique, Série Médecine, Bd. 5, 2. Teil, Paris 1972.

Prange, A.J. and Wilson, I.C.: Thyrotropin releasing hormone (TRH) for the immediate relief of depression: A preliminary report, Psychopharmacologia 26 suppl.: 82, August 1972.

Prange, Jr., A.J., Lara, P.P., Wilson, I.C., Alltop, L.B. and Breese, G.R.: Effects of thyrotropin-releasing hormone in depression, Lancet, 999-1002, November 11, 1972.

Prange, A.J.: Therapeutic and theoretical implications of imipramine-hormone interactions in depressive disorders in psychiatry. Proceedings of the V World Congress of Psychiatry. De la Fuente, R. and Weisman, M.N., editors: Excerpta Medica, Amsterdam, 1973, 1023-1031.

Prange, A.J., Lipton, M.A., and Wilson, I.C.: Clinical intimations of amine balance and permission. Psychopharmacology Bull. 10/3: 53-55, July 1974.

Prien, R.F., Klett, C.J., and Caffey, Jr., E.M.: Lithium carbonate and imipramine in prevention of affective disorders, Arch. Gen. Psychiat., 29: 420-425, 1973.

Rack, P.H.: Clomipramine (Anafranil) in the treatment of obsessional states with special reference to the Leyton obsessional inventory, J. Int. Med. Res. 1: 397-402, 1973.

Rafaelsen, O.J. and Gram, L.F.: Interaction between antidepressants and other groups of psychopharmaca, in Symposia Medica Hoechst (9), editors: Classification and Prediction of Outcome of Depression, F.K. Schattauer Verlag GmbH., Stuttgart, Germany, 1974, 253-256.

Raskin, A.: Drugs and depression subtypes, in Depression in the 70's, Excerpta Medica, 1971.

Reil, J.C.: Rhapsodien über die Anwendung der psychischen Curmethode auf Geistes-zerrüttungen, 2. Aufl., Halle 1818 (1. Aufl. 1803).

Rigby, B., Clarren, S. and Kelly, D.: A psychological and physiological evaluation of the effects of intravenous clomipramine (Anafranil), J. Int. Med. Res. 1, 308-316, 1973.

Robin, A.A., and Langley, G.E.: A controlled trial of imipramine, Brit. J. Psychiat. 110: 419-422, 1964.

Robinson, D.S., Nies, A., Ravaris, C.L., Ives, J.O., Lamborn, K.R.: Treatment response to MAO inhibitors: Relation to depressive typology and blood platelet MAO inhibition, in Symposia Medica Hoechst (8), editors: Classification and Prediction of Outcome of Depression, F.K. Schattauer Verlag GmbH. Stuttgart, Germany, 1974, 259-267.

Rybakowski, J.: Lithium carbonate in endogenous depression, Psychiat. Pol. 6/5: 547-550, 1972.

Sano, I.: L-5-hydroxytryptophan (L-5-HTP) treatment in endogenous depression, Munch. Med. Wschr. 114/40, 1713-1716, 1972.

Sargant, W.: Treatment of anxiety states and atypical depressions by the monoamine oxidase inhibitor drugs, J. Neuropsychiat. 3 (Suppl.): S96-102, 1962.

Schildkraut, J.: Norepinephrine metabolites as biochemical criteria for classifying depressive disorders and predicting responses to treatment: Preliminary findings, Am. J. Psychiat. 130/6: 695-698, 1973.

Sethna, E.R.: A study of refractory cases of depressive illnesses and their response to combined anti-depressant treatment, Brit. J. Psychiat. 124: 265-272, 1974.

Sjöqvist, F.W., Hammer, W., Ideström, C.M., Lind, M., Tuck, D. and Asberg, M.: Plasma level of monomethylated tricyclic antidepressants and side effects in man. Proceedings of the European Society for Study of Drug Toxicity, Paris 1967, International Congress Series Number 145, Excerpta Medica, Amsterdam, 246-253, 1968.

Spear, F.G., Hall, P. and Stirland, P.: A comparison of subjective responses to imipramine and tranylcypromine, Brit. J. Psychiat., 110, 53-55, 1964.

Stein, L.: Psychopharmacological substrates of mental depression. Proceedings of the First International Symposium on Antidepressant Drugs, Milan, April 1966, Excerpta Medica, International Congress Series No. 122, 130-140.

Steinberg, D.L.: Hematoporphyrin treatment of severe depressions, Am. J. Psychiat., 92: 901-913, January 1936.

Stockley, I.H.: Drug interactions: 5 tricyclic antidepressants. Pt. 1. Interactions with drugs affecting adrenergic neurones, Pharmaceutical Journal 208: 559-562, 1972.

Tan, E., Marks, I.M. and Marset, P.: Bimedial leucotomy in obsessive compulsive neurosis: A controlled serial enquiry, Brit. J. Psy[illegible], 118: 155-164, 1971.

Van Praag, H.M., Korf, J., Dols, L.C.W., and Schut, T.: A pilot study of the predictive value of the probenecid test in application of 5 hydroxytryptophan as antidepressant, Psychopharmacologia (Berl.) 25/1: 14-21, 1972.

Warnes, H., Lehmann, H.E., and Ban, T.A.: Adynamic ileus during psychoactive medication: A report of three fatal and five severe cases, Canad. Med. Ass.J. 92: 1112-1113, 1967.

Washburne, A.C.: Nicotinic acid in depressed states: preliminary report, Ann. Int. Med. 32: 261-269, February, 1950.

West, E.M. and Dally, P.J.: Effects of iproniazid in depressive syndrome, Brit. Med. J.I: 1491-1494, 1959.

Wharton, R.N., Perel, J.M., Dayton, P.G., and Malitz, S.: A potential clinical use for methylphenidate with tricyclic antidepressants, Am. J. Psychiat. 127: 12, 1971.

Whiting, B., Golbert, A., and Waldie, P.: The drug disc warning to drug interaction, Lancet 1 (7811): 1037-1038, 1973.

Wittenborn, J.R.: Factors which qualify the response to iproniazid and imipramine, in Wittenborn, J.R., and May, P.R.A., editors: Prediction of Response to Pharmacotherapy, Charles Thomas, Springfield, Ill., 1966.

Wittenborn, J.R.: Diagnostic classification and response to imipramine. Unpublished manuscript, 1967.