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CLINICAL PHARMACOLOGY OF IMIPRAMINE AND RELATED ANTIDEPRESSANT COMPOUNDS[1]

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I. INTRODUCTION

A. Aims and purposes

In this paper, we review the clinical pharmacology of imipramine and related antidepressant drugs. Among the various drugs currently used for the treatment of depression, imipramine and related compounds are generally considered to be

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the most effective agents (60, 71, 260, 327). The choice of imipramine as the topic of this review paper is prompted, however, not only by its clinical efficacy, but also by two other considerations: first, a discussion of the clinical pharmacology of imipramine highlights a number of important methodological issues in the evaluation of antidepressant drugs; and second, the lack of a clearly understood mode of action for imipramine has been a potent stimulus for much current investigation.

For these reasons, a review of the clinical pharmacology of imipramine seems appropriate at this time. In preparing this paper, we surveyed publications in English intensively; sources in other languages received less attention. Special attention was given to studies of possible modes of action, particularly those contributing to an understanding of drug effects in depressed psychiatric patients.

In the brief history of drug treatment of depression, clinical effect has almost always been discovered by accident rather than having been predicted from animal studies. The efficacy of two main classes of antidepressant drugs currently in use, the monoamine oxidase (MAO) inhibitors and the imipramine derivatives, was not predicted from the then available animal psychopharmacology. Previously, the main criterion for predicting clinical antidepressant activity was that derived from experience with the amphetamines; that is, drugs were screened for antidepressant activity on the basis of their capacity to increase the gross psychomotor activity of laboratory animals. By this criterion, neither the MAO inhibitors nor the imipramine derivatives were predicted to be antidepressant drugs; and the demonstration of their clinical efficacy has stimulated the creation of animal models of clinical depression on the basis of which antidepressant therapeutic activity of new agents could be predicted and, more significantly, the modes of action of current agents could be better understood. This example of antidepressant drugs exemplifies the "heuristic value of psychiatry," to use Kety's phrase (172).

In retrospect, it was unlikely that drug-induced changes in baseline behavior would be useful predictors of drugs for psychiatric disorders. It is more reasonable to expect that drugs useful for psychiatric disorders should influence some altered behavioral or neuropharmacologic state of the animal. Recently, animals whose amines have been depleted by prior administration of reserpine or other compounds have proved useful as a research model of depression. Interesting hypotheses have been proposed as to the possible modes of action of antidepressant drugs. A number of these hypotheses relate imipramine's antidepressant actions to effects on brain catecholamines, not through enzymatic inhibition as occurs with the MAO inhibitors, but by altering membrane permeability of the storage granule or adrenergic receptor. If these hypotheses are confirmed, a general theory of antidepressant drug action may emerge.

B. The classification of antidepressant drugs

For many decades, drugs like the barbiturates, chloral hydrate, or bromide had been used to treat the insomnia, anxiety, agitation, and related features of depression. In the late 1930's, numerous drugs resembling amphetamine were

introduced for the symptomatic relief of mild depressive states (6, 172). Electroconvulsive therapy (ECT), introduced in 1938–1940, proved useful in selected cases and many severe depressions are still successfully treated with it (6, 165). When the phenothiazines, the Rauwolfia alkaloids, and related compounds became available in 1952–1954, they were widely prescribed in the treatment of depression, especially when symptoms such as agitation, insomnia, anxiety, and restlessness were prominent features of the depressive symptomatology (72, 94, 165, 190). The consensus was that they were relatively ineffective against the "core" symptoms of guilt, worthlessness, retardation, and depressed affect, but this view has recently been questioned. (This problem will be reviewed in Section IV E.)

In 1957, the MAO inhibitors and imipramine were introduced almost simultaneously. Since then over a dozen new antidepressant compounds have been investigated. The specifically antidepressant drugs can be classified into three major groups, as shown in Table 1.

TABLE 1
Classification of antidepressant drugs

General Group	Generic Name	Trade Name
I. Amphetamine-like compounds		
A. Amphetamines	amphetamine	Benzedrine
	dextroamphetamine	Dexedrine
	methamphetamine	(many)
B. Others	benactyzine	Suavitil
	deanol	Deaner
	methylphenidate	Ritalin
	pipradrol	Meratran
II. Monoamine oxidase inhibitors		
A. Hydrazines	iproniazid	Marsilid*
	isocarboxazid	Marplan
	nialamide	Niamid
	phenelzine	Nardil
	pheniprazine	Catron*
B. Nonhydrazines	etryptamine	Monase*
	pargyline	Eutonyl
	tranylcypromine	Parnate
III. Tricyclic compounds		
A. Iminodibenzyls	desipramine	Pertofrane
	imipramine	Norpramin
		Tofranil
	opipramol	Ensidon*
B. Dibenzocycloheptenes	amitriptyline	Elavil
	nortriptyline	Aventyl
	protriptyline	Vivactil*
C. Thioxanthenes	chlorprothixene	Taractan

* Not available for prescription use in U.S.A.

In proposing this classification, we recognize that the categories are based on varying biochemical and pharmacological criteria. A single frame of reference should prevail in any ideal classification. However, since these three groupings seem to have wide usage and reflect many common characteristics of the drugs within each class, we have provided this classification so that imipramine and its derivatives may be viewed in the larger picture of antidepressant drug treatments.

II. GENERAL PHARMACOLOGY

A. Historical background

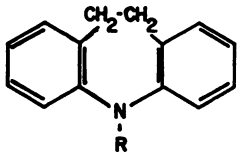
According to Hafliger (129), iminodibenzyl, the parent compound of imipramine, was synthesized in 1899 by Thiele and Holzinger. Although many of the chemical characteristics of the compounds were described, relatively little attention was paid to its pharmacology until 1948, when a number of heterocyclic compounds, including iminodibenzyl derivatives, were synthesized as potential antihistaminic agents (278). In the pharmacologic testing of these compounds, antihistaminic and atropine-like actions were observed and some compounds showed hypnotic and analgesic properties (128). The first compound chosen for clinical investigation, G-22150, had some hypnotic activity but was not as potent in this action as the barbiturates. Meanwhile, the demonstration of the antipsychotic effects of the phenothiazines stimulated interest in the iminodibenzyl derivatives because of their structural similarity to the phenothiazines and common pharmacologic properties, particularly the prolongation of the unconsciousness produced by barbiturate.

For these reasons, the initial clinical trials with imipramine were carried out in chronically schizophrenic and other psychotic patients. In 1954, R. Kuhn observed that while there was little antipsychotic action, elevation of the mood of depressed patients was evident (197, 198). Considerable credit must be given to Kuhn for his skill as a clinical observer and for his persistence. The available data gave no indication of the possible antidepressant effects of imipramine. On the contrary, all the indications were that it was similar to chlorpromazine. Yet, Kuhn's careful observations detected the new kind of antidepressant effect now considered characteristic of imipramine and related compounds.

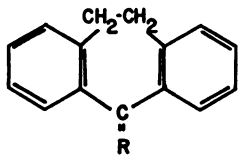
B. Chemical structural considerations

As shown in the structural formulas, imipramine, as an iminodibenzyl derivative, bears a close structural similarity to the phenothiazines, the only difference being that the sulfur atom bridging the two benzyl rings in the phenothiazine nucleus has been replaced by a CH_2—CH_2 group in the iminodibenzyl nucleus. According to Hafliger (129), the presence of the two-carbon chain serves as a barrier to the conjugation of the benzene rings and brings about asymmetry of the molecule. Many thioxanthene and dibenzocycloheptene compounds, also closely related both chemically and pharmacologically to the phenothiazines and to imipramine, are reported to have clinical usefulness in depressed and psychotic patients (182). However, little is known about the mechanisms relating the struc-

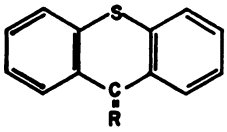
STRUCTURAL FORMULAS OF IMINODIBENZYL AND RELATED COMPOUNDS



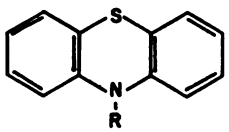
IMINODIBENZYL



DIBENZOCYCLOHEPTENE



THIOXANTHENE



PHENOTHIAZINE

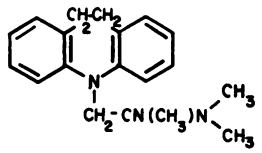
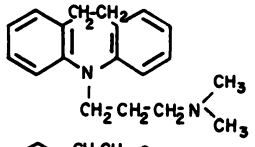
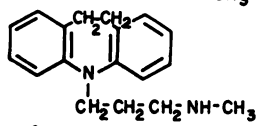
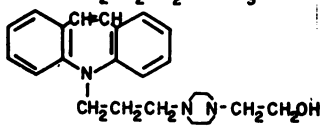
tures of these compounds to their differences in biological activities. Because of their many common properties, the iminodibenzyls, dibenzocycloheptenes, and thioxanthenes are usually referred to as the "tricyclic antidepressants."

1. The iminodibenzyl derivatives. Several iminodibenzyl derivatives have undergone clinical evaluation, and two, imipramine and desipramine, are available for prescription use.

Imipramine, the compound in this group first shown to have clinical efficacy, remains the prototypical compound. In animals, it produces motor retardation, prolongation of barbiturate sleep, slowing of the cortical EEG, and atropine-like effects. Because these actions are very similar to those of chlorpromazine, many recent investigations have been devoted to delineating the differences between the imipramine-like compounds and the phenothiazines. Unlike the phenothiazines, imipramine reverses many of the characteristic psychomotor and autonomic effects of reserpine. Another important difference between the phenothiazines and imipramine is imipramine's potentiation of central and peripheral adrenergic mechanisms, a topic which will be reviewed in greater detail later in Sections II E and II H.

Desipramine (also called desmethylimipramine or DMI) was isolated in 1960 by Herrmann and Pulver (141). The animal pharmacology in many respects resembles that of the parent compound (35, 45, 309). Unlike imipramine, desmethylimipramine exerts no direct effects on alertness and psychomotor activity in rats (309). It is particularly potent in reversing the reserpine-like syndrome (114), and Brodie and his associates have suggested that the pharmacologically active form of imipramine may be desmethylimipramine (45, 114, 314). In certain

IMINODIBENZYL DERIVATIVES

Generic Name	Trade Name	Chemical Structure
G- 22150	——	
Imipramine	Tofranil	
Desipramine	Norpramin Pertofrane	
Opipramol*	Ensidon	

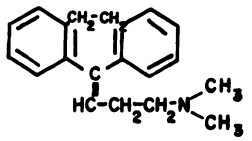
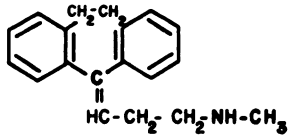
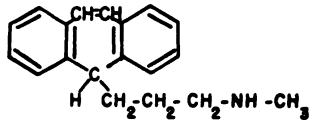
*An iminostilbene derivative, not an iminodibenzyl derivative

species, the antireserpine action comes on more rapidly with desmethylimipramine than with imipramine, and from this, quicker onset of clinical action has been predicted (222). Early clinical studies have only partially confirmed these predictions (25, 28, 108, 154, 216, 231, 244).

Opipramol, also called Ensidon, an iminostilbene derivative with a piperazine side chain, was synthesized in part because of the high potency of the piperazine derivatives of the phenothiazines. Preliminary clinical reports by Azima (25) indicated that the drug has a clinical pharmacologic spectrum very similar to that of imipramine. Kiloh (181), however, observed that it was less effective than imipramine. It is uncertain whether the drug will be marketed in the United States.

2. Amitriptyline and other dibenzocycloheptene derivatives. As shown below, the dibenzocycloheptene structures closely resemble that of imipramine and also that of phenothiazine. The actions of amitriptyline, the first dibenzocycloheptene derivative introduced to clinical use, have been reviewed extensively by Vernier and his associates (322, 323, 324). This compound has adrenergic potentiation actions as well as atropine-like effects (290). It produces depressant effects on the cortical EEG, as well as reduction in spontaneous motor behavior. Amitriptyline antagonizes the sedation induced by tetrabenazine and also the hypothermia induced by reserpine in mice (323). In common with other drugs in this series, there is intensification of the vasopressor response to norepinephrine and also potentiation of the effects of amphetamine on various forms of operant conditioning behavior. Vernier feels that the effects on the reserpine state and the poten-

DIBENZOCYCLOHEPTENE DERIVATIVES

Generic Name	Trade Name	Chemical Structure
Amitriptyline	Elavil	
Nortriptyline	Aventyl	
Protriptyline	Vivactil	

tiation of pressor amines are related to the antidepressant actions of the tricyclic compounds, while the effects of amitriptyline on psychomotor behavior and on the EEG which resemble those of the phenothiazines (323) are related to the hypnotic actions seen clinically.

Clinical reports have been very favorable (29, 47, 79, 80, 110, 167, 229, 250, 320, 330, 331). A number of excellent controlled clinical trials have established this drug as equal to and perhaps slightly more effective than imipramine (51, 160, 161). These studies will be reviewed in some detail below (see Section IV C).

Two other dibenzocycloheptene derivatives, nortriptyline and protriptyline, also have received clinical attention. Nortriptyline (Aventyl), the desmethyl derivative of amitriptyline, has recently been approved for prescription use. Preliminary pharmacologic data were reported in animals (255, 323) and man (162); its clinical pharmacology is very similar to that of the other compounds in this series. It is considerably more potent than amitriptyline, the average dose being 20 to 80 mg per day as compared to 100 to 200 mg per day of amitriptyline. A few clinical reports have appeared, but as yet no controlled trials have been reported (32, 33, 232).

More recently, animal studies and clinical reports have appeared on protriptyline (previously known as animethyline and to be marketed as Vivactil) (9, 21, 81, 90, 91, 319). In general, its pharmacologic profile resembles those of the other members of this series, but the clinical reports are only preliminary. Protriptyline is even more potent than nortriptyline, the average clinical dose being 10 to 40 mg per day. There are reports that it stimulates psychomotor activity, producing restlessness and insomnia, in contrast to amitriptyline, which possesses hypnotic actions.

3. Thioxanthenes. Although in American and British writings the thioxanthenes are not usually listed among the antidepressant compounds, they deserve mention

in this review for two reasons: first, in chemical structure and pharmacological actions they are closely related to the phenothiazines and to the other tricyclic antidepressants; and second, French and German clinical observers have reported antidepressant effects in selected patients. In the thioxanthene ring structure, a carbon atom with a double bond to the side chain has replaced the ring nitrogen in the phenothiazines. This structural change is claimed to account for its broader range of actions and lower toxicity. Chlorprothixene (Taractan), the thioxanthene which has received the most extensive studies, is similar to chlorpromazine in behavioral effects, EEG actions, hypotensive effects, anti-emetic activity, and prolongation of the effects of barbiturates, ethanol and ether (106, 112, 240). Clinical reports, mostly uncontrolled, have emphasized reduction of psychomotor agitation, anxiety, insomnia, aggressiveness, delirium, and hallucinations. One small controlled study indicated efficacy greater than placebo in psychotic patients (168). Of special note are the reports of antidepressant effects (40, 89, 259). Detailed comparisons with imipramine or other antidepressants, however, are necessary before antidepressant activity can be regarded as established.

C. Absorption, distribution, metabolism, and excretion

The various compounds in this series are readily absorbed from the gastrointestinal tract or when administered parenterally. Measurable concentrations of imipramine may be found in human plasma 30 minutes after intramuscular injection of 100 mg, after which plasma levels fall off rapidly (141). Some information is available about the distribution of the compound in different organs. In the rabbit, higher levels are found in heart muscle than in skeletal muscle (115, 129). Limited data from human subjects indicate relatively high concentrations of imipramine in liver, brain and lungs, a distribution similar to that observed for phenothiazines (76, 77).

Considerable attention has been given to the metabolism of imipramine because of the possible usefulness of the desmethyl derivative as an antidepressant compound (35, 252). The major pathways of imipramine metabolism involve hydroxylation and N-demethylation as well as conjugation with glucuronide (96, 141). Recent work emphasizes marked species and sex differences in the metabolism and in the organ distribution of these compounds, possibly related to the speed of various enzymatic transformations (34, 77, 251, 253). The urine of patients treated with imipramine contains only small amounts of the administered drug in the form of iminodibenzyl derivatives, including unchanged imipramine, the hydroxylated metabolite, and what are probably the desmethyl metabolites (140). It is probable that amitriptyline and related compounds are metabolized in similar ways. These pathways are similar in most respects to those of the metabolism of chlorpromazine (57).

D. Effects on the central nervous system

In the EEG's of rabbits and cats, intravenous doses of imipramine (3 to 10 mg/kg) produced slow waves and occasional spindles (231, 287). Similar effects

are seen in man (92, 179). The EEG arousal on peripheral painful stimulus in rabbits is blocked by imipramine (144, 145, 146).

The severity of seizures in rabbits evoked either by electroshock or by Metrazol (pentylenetetrazol) is diminished by imipramine (241). No significant influence, however, was noted on the fatal outcome of seizures induced by strychnine. In contrast, chlorpromazine does not alter the various components of convulsions due to electroshock or Metrazol. However, further EEG studies in cats (321) and rabbits (303) indicated that imipramine can evoke seizure-like patterns in the rhinencephalon and other structures. The occurrence of seizures in patients treated with imipramine (Section V B) may be related to this effect (179).

Shagass (281) has recently reviewed the clinical electrophysiology of depression and summarized the evidence that depressive states may involve changes in cortical excitability often related to alterations in body electrolyte distribution. In recent years, sensory evoked potentials techniques have been developed for clinical research; and there are indications that the effects of imipramine on these potentials are more pronounced in depressed patients than in normal subjects (282, 283, 301). The significance of these neurophysiological actions for antidepressant effects is unclear at this time.

E. Effects on autonomic nervous system

Considerable research has been carried out on the effects of imipramine and related compounds on autonomic functions. They have no direct effects upon blood pressure, pulse or EKG; but they have a number of actions on autonomic effectors, particularly atropine-like effects and, more significantly, indirect effects on blood pressure by interaction with various compounds (287, 289). Many of these effects on peripheral autonomic functions were noted in the early pharmacological studies by Domenjoz and Theobald (78) and by Sigg (287). On the basis of these observations, Sigg proposed that the potentiation of adrenergic effects noted peripherally might also occur centrally, perhaps through sensitization of the adrenergic receptor to norepinephrine (288). The evidence subsequently developed in support of this hypothesis will be discussed in Sections II F and II G. In this section, we shall review the findings from studies of peripheral autonomic functions.

1. Atropine-like effects. Small doses of imipramine (1 to 3 mg/day) in cats diminish the bradycardia following stimulation of the peripheral cut vagus and reduce pilocarpine-induced salivation, and on the isolated intestine imipramine blocks the effect of acetylcholine (287). These atropine-like effects undoubtedly underlie many of the side effects observed clinically, such as dry mouth, constipation, and blurring of vision.

Imipramine also may block the centrally mediated increase in parasympathetic output, as evidenced by a reduction of the rate of salivation (313). Indirect evidence for central atropine-like effects was offered by Fink from studies of the effects of acute administration of imipramine on the EEG of normal subjects. He reported desynchronization and an increase of *theta* rhythms on the EEG in conjunction with feelings of relaxation and lassitude; these effects are similar to those of atropine (92, 93).

2. Effect of adrenergic systems. Sigg and his associates have reported extensive studies on the nictitating membrane of the cat, particularly of interactions of imipramine with other drugs (291). Imipramine, but not the phenothiazines, potentiates many of the actions of catecholamines and serotonin on this organ (234, 288). This potentiation is not due to circulating catecholamines released from the adrenal medulla (78, 290, 296).

Although imipramine has almost no direct vasopressor action, significant interactions occur with various sympathomimetic amines (54, 111, 142, 272, 291). Imipramine potentiates the blood pressure rise after norepinephrine, whereas the pressor response to epinephrine is less affected (290). In contrast, the rise in blood pressure produced by the indirectly acting vasopressor amines, tyramine, amphetamine, and phenethylamine, is blocked by imipramine (287) and also by amitriptyline (283). Following the formulation of Burn and Rand (50), it is generally held that the indirectly acting sympathomimetic amines affect blood pressure through release of norepinephrine stores. Similar blocking actions have been described for cocaine, methylphenidate, and tripelennamine (221). Catecholamine-depleting agents such as reserpine and guanethidine also block the vasopressor action of these indirectly acting amines, but, as reviewed by Green (123), the pattern of their actions is different from that of imipramine. Since the members of the imipramine-amitriptyline class of antidepressants do not deplete catecholamine from tissues, including brain, their blocking of the vasopressor effect of the indirectly acting sympathomimetic amines may be due to membrane effects on storage sites or receptor organs (233, 272, 288, 305, 306). This view is consistent with results of experiments on effects of imipramine on uptake and storage of catecholamines as discussed in Section II F 3.

F. Effects on monoamines in the brain

1. Relevance of monoamines to depression. Over the past two decades, there has been a gradual accumulation of evidence suggesting a probable association between the disorders of affect (depression and elation) and changes in monoamine metabolism in the brain. Space does not permit a complete treatment of this topic here, and the interested reader should consult the many reviews of this area (44, 83, 86, 188, 333).

The evidence for this view is almost entirely indirect, being derived from observations that most of the agents affecting behavior and mood also have profound actions on the indoleamines and the catecholamines of the brain and their metabolism. Soon after reserpine and other Rauwolfia derivatives were observed to calm excited psychotic patients, including manic patients (see 62, 190), they also were found to reduce levels of stored and free amines in the brain, in particular serotonin and norepinephrine (see 286). Moreover, reserpine produces severe depressive reactions, particularly in patients with hypertension (4, 134, 227). It was postulated that the behavioral action of the Rauwolfia derivatives was secondary to their effects upon these amines in the brain. The claims that iproniazid, a monoamine oxidase inhibitor, alleviated some depressions (67, 176, 189) lent further support to the concept that depressive states might be associated with de-

ficiency in brain amines (67, 189, 191). Although the importance of the monoamine oxidase system in catecholamine degradation has undergone considerable revision following the demonstration of the catechol-O-methyl-transferase pathway, therapeutic changes with the MAO inhibitors when they occur are still believed to be related to drug-induced changes in brain amines (8, 12, 192, 286). As is well known, the relative roles of catecholamines and indoleamines in regulation of behavior and mood have been the subject of considerable discussion, although the current consensus favors the catecholamines as the more important substances (44, 46, 55, 85, 86, 297).

2. Brain levels of monoamines. With the claims that many MAO inhibitors were clinically effective as antidepressants, it seemed logical that imipramine might exert its action through inhibition of the MAO system or some other enzyme systems involved in the metabolism of amines. Numerous studies demonstrated however, that imipramine does not inhibit the MAO system or the O-methyltransferase system (242, 243, 252).

Goldstein and Contrera reported that imipramine *in vitro* inhibits dopamine-β-hydroxylase, the enzyme that catalyzes the conversion of dopamine to norepinephrine (119, 120). However, studies on the direct effects of imipramine on brain levels of various amines, particularly serotonin, norepinephrine, and dopamine indicate that neither imipramine nor its related compounds alter brain levels of these amines (43, 310, 311). This finding suggests that, while imipramine may have some effect on dopamine-β-hydroxylase, this does not influence brain levels of serotonin or norepinephrine. However, it is of note that almost all of these studies have been of acute drug effects. In view of the findings to be discussed below, studies of the effects of chronic administration of imipramine on brain amines would be of considerable interest.

3. Storage and uptake of amines. Studies of the uptake and storage of norepinephrine suggest other possible mechanisms for the effects of imipramine on peripheral autonomic functions and central adrenergic mechanisms. As reviewed by Kopin (192), norepinephrine is stored in at least two pools, one firmly bound and released by reserpine, the other loosely bound and released by sympathomimetic drugs (193, 317). Loosely bound norepinephrine, when released, leaves the cell in active form and is largely converted by O-methylation to normetanephrine or inactivated by rebinding. Firmly bound norepinephrine, released either spontaneously or by reserpine, is mainly inactivated by mitochondrial monoamine oxidase before leaving the cell (192, 194).

Imipramine has been found to interfere with the uptake by tissues of infused norepinephrine. This fact supports the view that imipramine acts by decreasing the membrane permeability of the cell or of the storage granule to this amine (13, 14, 73, 249, 316). Impiramine's action blocking the uptake of norepinephrine was first shown in peripheral tissues by Axelrod *et al.* (14), and in brain slices by Dengler and Titus (73). These effects are shared by other drugs, including cocaine and chlorpromazine (12, 73). Recently, Glowinski and Axelrod (116) have demonstrated inhibition of uptake of tritiated norepinephrine in intact rat brain by imipramine, desmethylimipramine and amitriptyline, but not by chlorpromazine.

At least two separate mechanisms of imipramine's action on norepinephrine may be involved: inhibition of uptake into storage granules and blocking of inactivation at adrenergic receptors (315).

4. Monoamine metabolism in depressed patients. In view of these findings in animals, it is unfortunate that only a few studies of monoamine metabolism have been undertaken in depressed patients. As reviewed by Durrell and Schildkraut (83), the available data are limited and inconclusive, particularly when urinary amines have been measured.

More promising data have emerged from studies of the effects of antidepressant drugs on catecholamine metabolism. The most extensive data are on drug effects on vanillylmandelic acid (VMA), which is the major, but not exclusive, urinary metabolite of both norepinephrine and epinephrine. Under normal circumstances, VMA is probably derived predominantly from norepinephrine, formed from this catecholamine through O-methylation and oxidase deamination (192). Decreased VMA excretion has been demonstrated by Von Studnitz in normal subjects (325) and by Resnick in schizophrenic patients following the administration of iproniazid, a monoamine oxidase inhibitor (257). Treatment with iproniazid and other MAO inhibitors, moreover, decreases the conversion of infused epinephrine to VMA in schizophrenic patients. McDonald and Weise (210) found that acute administration of reserpine increases, while acute administration of chlorpromazine decreases VMA excretion, both in schizophrenic patients and in normal subjects. With prolonged treatment, however, Randrup (254) has reported a decrease in VMA excretion in schizophrenic patients receiving reserpine, but no change in VMA excretion in patients receiving chlorpromazine.

Schildkraut *et al.* (277) have shown that clinically effective doses of imipramine and a MAO inhibitor decrease VMA excretion in depressed women. In addition, imipramine probably also alters urinary excretion of other catecholamine metabolites, including metanephrine (183, 275), and these changes seem to parallel the patients' clinical course. These effects may indicate decreased synthesis of norepinephrine; however, it is more likely that the imipramine effects are mediated by changes in membrane permeability reducing the amount of norepinephrine normally inactivated by deamination. Such a mechanism would provide a common action for imipramine and the MAO inhibitors by increasing the amounts of catecholamines available for functional action at adrenergic receptor sites. These views are admittedly speculative and much research is indicated to correlate clinically observed effects on amine metabolism with the known actions on adrenergic mechanisms.

G. Interactions with other drugs

In recent years, new pharmacological procedures have been developed involving interaction of the imipramine series of compounds with reserpine, tetrabenazine, amphetamines, or other agents having effects on behavior and on brain amines. To a great extent, the impetus for their development resulted from the failure of previous techniques to predict the antidepressant actions of imipramine and to distinguish the actions of imipramine from those of the phenothiazines.

1. Interactions with reserpine and other amine depletors. Animals under the influence of drugs such as reserpine, tetrabenazine, or guanethidine, which deplete amines in the brain or peripheral tissues, have proved to be very fruitful for testing new compounds suspected to have antidepressant properties (58, 66, 109). From the psychiatric view, the amine-depleted animal is of particular interest since it may provide a possible experimental analog of depression, especially since reserpine and possibly also *alpha*-methyldopa, both amine depletors, may produce depression in man.

As is well known, reserpine profoundly reduces the psychomotor behavior of animals. Sulser and his associates observed that imipramine and its metabolite, desmethylimipramine, reverse this effect (309, 312). Imipramine also reverses the sedative effects of tetrabenazine, another depletor of brain amines (314). Previously, many investigators had demonstrated that imipramine antagonizes many other actions of reserpine, especially its autonomic effects, without affecting reserpine-induced depletion of brain amines (58, 66, 78, 109). In animals the catecholamines of whose brains are selectively depleted prior to administration of reserpine, imipramine no longer antagonizes the behavioral effects of reserpine. This finding suggests that these actions of imipramine are dependent on the presence of catecholamines somewhere in the brain (274, 311). Pöldinger (244) has applied this concept clinically and reported that depressed patients who do not respond to imipramine alone improve on combination of reserpine and imipramine; the inference is that the release of amines by reserpine allows for greater action by imipramine.

2. Dopa reversal of reserpine state. Indirectly relevant to the research on the effects of imipramine on the adrenergic elements in the brain are the experiments in which dopa was used to modify or reverse the effects of reserpine. Dopa has been investigated for a number of years because of its role in the synthesis of norepinephrine and other catecholamines (105). Unlike norepinephrine, dopamine, or serotonin, dopa given to animals will cross the blood-brain barrier and increase amine concentration in the brain (328). In animal studies, dopa, but not 5-hydroxytryptophan, the amino acid from which serotonin is formed, reverses both the behavioral defects and the depletion of brain amines that follow the administration of reserpine. These actions of dopa are significantly potentiated by pretreatment of the animal with a monoamine oxidase inhibitor. Moreover, Everett has reported that imipramine, amitriptyline, and their desmethyl derivatives potentiate these actions of dopa and MAO inhibitors on the reserpine state (85). These findings support the hypothesis that the catecholamines rather than serotonin are involved in the behavioral components of the reserpinized depressed state (86, 102, 297, 308).

3. Clinical trials with monoamine precursors. Clinical investigations of possible therapeutic effects of amino acid precursors of norepinephrine and serotonin, however, have been inconsistent with the view that the catecholamines are the predominant monoamine whose metabolism is altered in depressed states. Klerman *et al.* (188) conducted clinical trials of dopa alone and dopa in combination with a MAO inhibitor in depressed patients, as an indirect test of the theory that

brain catecholamines are deficient in depressed states. Neither treatment significantly affected the depression, at doses with which cardiovascular effects, including hypertensive reactions, were observed in patients treated with both dopa and MAO inhibitor (276). Whether sufficient dopa entered the brain in these studies is uncertain. On the other hand, synergistic effects of tryptophan or 5-hydroxytryptophan combined with MAO inhibitors have been reported (65, 83, 191, 238), indicating that the indoleamines cannot be ruled out in any comprehensive formulation.

4. Interaction between imipramine and amphetamines. Studies of the interactions between imipramine and the amphetamines are of particular importance to the thesis that imipramine has central adrenergic effects. The amphetamines have for a number of years been used in the treatment of depressions, particularly the less severe clinical forms (122). In current concepts, the adrenergic action of amphetamine is attributed to release of norepinephrine. Recent studies have indicated that imipramine potentiates the behavioral effects of amphetamine in a variety of experimental situations (56, 274, 298, 299, 300, 301, 302, 332). This potentiation by imipramine occurs at low to moderate doses, while at higher doses there may be blocking (299, 332). Similar patterns are observed for chlorpromazine, but Stein (298, 299, 300) showed that with chlorpromazine this antagonism occurs at a lower dose than with imipramine, and that the dose margin between potentiation and antagonism is narrower with chlorpromazine than with imipramine. Further studies, especially those by Lapin, indicated that the effects of imipramine and chlorpromazine on the toxic effects of amphetamine on animals in group situations are mediated by a common mechanism (200). Hill *et al.*, studying timing behavior motivated by hunger, found that imipramine and desmethylimipramine potentiate the effects of methylphenidate, another centrally acting adrenergic agent (143). Using an operant conditioning mechanism, Stein and Seifter (301, 302) found that imipramine augments and prolongs the rewarding effects of amphetamine with hypothalamic stimulation, whereas chlorpromazine blocks this effect. Since atropine also potentiates some of these effects of amphetamine and of methylphenidate, Sigg argued that the atropine-like and adrenergic actions of imipramine probably work in the same direction (289). However, atropine has no effect on the reserpine state nor does it influence the effects of amphetamine on hypothalamic stimulation. These studies of differential drug effects on the response to hypothalamic stimulation are important evidence for central adrenergic actions of the imipramines, probably involving the diencephalon.

H. Behavioral studies

The initial studies of imipramine in animals revealed behavioral effects similar to those produced by chlorpromazine (78). At high doses (10 to 40 mg/kg) in cats, there was inhibition of psychomotor activity and reduced alertness. In mice, the compound increased the tendency to fall off the rotating cylinder and could antagonize isolated-induced aggressive behavior. In both these respects, however, the ED50 of imipramine was substantially greater than that of chlorpromazine.

In a number of other effects, including lengthening of hexobarbital and alcohol sleep time, lowering of body temperature, and effects on condition avoidance taken in rats, imipramine seemed like a weak phenothiazine (287, 288).

Advanced psychological techniques, particularly operant conditioning, have been widely applied to the study of various antidepressant compounds (63, 64, 74, 132, 195, 333). Early studies emphasized similarities between the antidepressant compounds and the phenothiazines, but recently developed techniques suggest behavorial actions which differentiate imipramine from the phenothiazine and which may be related to antidepressant actions. For example, amitriptyline and imipramine are similar to chlorpromazine in their effect on various avoidance schedules (323), while imipramine and amitriptyline (but not phenothiazines) potentiate many of the actions of amphetamine and other stimulants (56, 143). Furthermore, Stein showed that the tricyclic antidepressants, but not chlorpromazine, lower the threshold doses of amphetamine in experiments with intracranial self-stimulation (299).

Drug effects on various perceptual, psychomotor and cognitive performance tests have been studied in normal subjects and depressed patients (75, 164, 245). Studies in normal subjects (75, 245) indicated little effect other than mild hypnotic actions and psychomotor retardation similar to effects occurring with the phenothiazines (187, 247). Attempts have been made to correlate clinical changes with psychological measures, but most of the changes observed also occur when symptoms are reduced in patients treated with ECT or without specific treatment; hence they are probably not drug effects (268, 269, 270, 340). The utility of these procedures in the clinical pharmacological study of antidepressants remains unclear.

III. CLINICAL EFFECTS

A. General considerations

At this time there are several major questions about the clinical actions of the tricyclic antidepressant drugs to which only partial answers are available. Are these drugs more effective than placebo in the treatment of depressed psychiatric patients? If so, how much more? With what kinds of depressed patients are they particularly useful? Do they diminish certain symptoms? If so, which ones? How do they compare with electroconvulsive therapy (ECT), the most effective previous somatic therapy? Are they more effective than other allegedly antidepressant drugs?

These and a number of related issues will be discussed in some detail in this section. Since the majority of the published controlled or comparative clinical studies concerns either imipramine or, to a lesser extent, amitriptyline, the discussion will of necessity focus on these drugs.

1. The importance of controlled studies: placebo effect. Many skeptics doubt that any of the so-called antidepressant drugs are "really" effective therapeutic agents, and argue that what clinical efficacy these drugs have is mediated by socio-psychological mechanisms, particularly the suggestibility and faith of the patient, the enthusiasm and zeal of the physician, or both. This general view is

represented in the writings of Henry K. Beecher (31) and Jerome Frank (99) and has been applied by Robert Liberman to antidepressant drugs (206). Partial substantiation of this viewpoint is found in the high rate of placebo response in depressed patients reported in many controlled clinical trials (124, 154, 157, 327).

2. The natural history of depressive reactions. In addition to placebo effects, another important factor which makes controlled studies of depression imperative is the natural history of these reactions. Depressions, on the whole, are among the psychiatric conditions with the best prognosis for symptomatic recovery, with or without treatment. Most depressive episodes are self-limited and consequently, the "spontaneous improvement rate" is usually quite high. Alexander (1953), in pooling a large group of clinical reports on the treatment of hospitalized depressed patients before modern pharmacotherapy, reported complete recovery or social improvement of 44% of patients within the first year and 56% recovery eventually over longer time periods (6). He also summarized data from over 2,000 patients treated with ECT and reported over 68% recovery within the first year. These improvement rates closely resemble those reported in most uncontrolled clinical studies and in many of the controlled studies on hospitalized patients. Many of these drugs are said to require one to three weeks to take full pharmacologic effect, a period which may allow for "spontaneous recovery," especially in mild depressive reactions occurring in response to untoward life events.

B. Clinical efficacy in depression

While the overall quality of the clinical literature is still only fair, there is an encouraging trend towards better designed and more carefully controlled studies. Although almost all clinical reports conclude that these drugs are highly useful and very effective, many of the controlled clinical trials have led to equivocal findings. Even when such findings have been favorable to the drug under study, the differences between the improvement rates of the drug-treated patients and

TABLE 2a

Summary of imipramine-placebo controlled clinical trials: studies reporting number of outpatients improving on each treatment

Authors	Diagnosis	Imipramine Dose (mg/day)	No. of Patients				Control Dose (mg/day)	Evaluation	Drug-Placebo Difference
			Imipramine		Control				
			Improved	Unimproved	Improved	Unimproved			
Abraham *et al.* (3)	Psychotic and neurotic	100	36	12	7	10	Inert substance	2 wk	Yes
Ball and Kiloh (27)	Psychotic	250	20	7	6	22	Inert substances	4 wk	Yes
Ball and Kiloh (27)	Neurotic	250	13	9	4	16	Inert substances	4 wk	Yes
Daneman (70)	Neurotic	200	73	21	16	85	Atropine 1.4 mg	4 wk	Yes
Uhlenhuth and Park (318)	Neurotic	150	9	13	6	14	Atropine 0.6 mg	2 wk	Yes

of the control group have not been as great as one might have anticipated from the reports of uncontrolled studies. Among the large number of clinical reports, there is fairly general agreement that significant improvement can be expected from the use of imipramine in 60 to 80% of various types of depression (15, 16, 17, 18, 22, 23, 26, 36, 42, 71, 88, 100, 101, 150, 152, 156, 170, 173, 175, 196, 201, 203, 205, 211, 214, 217, 246, 258, 273, 293, 304, 307).

1. Controlled studies. As shown in Tables 2a, 2b, and 3, there are now twenty-three published controlled studies in which imipramine was compared either with an inert substance or with another control drug (3, 11, 27, 70, 87, 94, 104, 125, 133, 151, 155, 170, 171, 205, 225, 237, 256, 261, 265, 269, 270, 271, 318, 329, 335, 340). Of these only five studies failed to show some statistically significant difference in the expected direction between drug and the control medication, although in several of these papers, the authors (256, 318, 329) felt that the study as a whole did not give particularly convincing evidence of imipramine's general superiority to the control. Tables 2a and 2b summarize those studies which reported their results in a manner that permitted the recovered patients and the markedly or moderately improved patients to be separated from the slightly improved, unchanged or worsened patients on both drug and control medication. Although the

TABLE 2b

Summary of imipramine-placebo controlled clinical trials: studies reporting number of hospitalized patients improving on each treatment

Authors	Diagnosis	Imipramine Dose (mg/day)	No. of Patients				Control Dose/Day	Evaluation	Difference
			Imipramine		Placebo				
			Improved	Unimproved	Improved	Unimproved			
Ashby and Collins (11)	Chronic psychotic	150	10	4	7	14	Inert substance	9 wk	No
Fahy *et al.* (87)	Psychotic	100	10	6	8	7	Thiopental sleep	3 wk	No
Fink (94)	Psychotic	300	9	2	4	6	Inert substance	6 wk	Yes
Friedman *et al.* (104)	Psychotic and neurotic	225	11	6	4	15	Inert substance	6 wk	Yes
Greenblatt *et al.* (124)	Psychotic and neurotic and schizophrenic	200	54	19	27	12	Inert substance	8 wk	No
Höhn *et al.* (151)	Psychotic and neurotic and schizophrenic	200	10	4	9	5	Inert substance	4 wk	No
Kenning *et al.* (170)	Psychotic and neurotic	200	21	17	5	7	Inert substance	4 wk	Yes
Leyberg and Denmark (205)	Chronic psychotic	250	18	2	2	18	Inert substance	2 wk	Yes
Miller *et al.* (225)	Chronic psychotic and neurotic and schizophrenic	200	7	17	1	22	Inert substance	4 wk	No
Rees *et al.* (256)	Psychotic	250	7	13	2	18	Inert substance	3 wk	Yes
Robin and Harris (264)	Neurotic	200	11	9	5	7	Inert substance	2 wk	Yes
Roulet *et al.* (271)	Neurotic	175	4	19	5	21	Inert substance	4 wk	No
Weintraub and Aronson (329)	Psychotic and neurotic	150	30	7	22	10	Atropine 0.3 mg	4 wk	Yes

TABLE 3

Summary of imipramine-placebo controlled clinical trials: studies reporting only average values on criterion measures for patient groups

Author	Diagnosis	Imipramine Dose (mg/day)	No. of Patients		Control Dose (mg/day)	Evaluation	Drug-Placebo Difference
			Imipramine	Control			
Hare *et al.* (133)	Psychotic and neurotic	150	78	78	*d*-Amphetamine 15 mg and amobarbital 150 mg	3 wk	Yes
Hollister (155)	Neurotic and depressed and schizophrenic	170	27	31	Atropine 1 mg	3 wk	No
Overall *et al.* (236)	Psychotic and neurotic	225	65	65	Inert substance	3 wk	Yes
Rickels *et al.* (261)	Neurotic	150	44	44	Inert substance	2 wk	Yes
Wilson *et al.* (335)	Psychotic	150	6	6	Thiopental	5 wk	No
Wilson *et al.* (335)	Psychotic	240	10	4	Thiopental	5 wk	Yes
Wittenborn *et al.* (340)	Neurotic	200	21	21	Inert substance	Discharge or 10 wk	Yes

reliability or comparability of these judgments cannot be proved, the table provides a useful view of work to date. One may note that 65% of the 550 patients treated with imipramine improved while 31% of the 459 control patients improved. On this basis, imipramine seems superior to placebo. On the other hand, some of the improved patients were not sufficiently improved to satisfy either the patient or the physician, and it may be inferred that imipramine is not an entirely satisfactory treatment in many of the depressed patients to whom it was given.

2. Use of atropine and controls other than inert substances. The use of atropine as a control medication posed interesting problems. In Daneman's study (70), carried out in private practice, only a 16% improvement rate was obtained in the group treated with atropine (1.4 mg per day). One wonders if the atropine could not have been having an adverse effect. On the other hand, the first Veterans Administration collaborative study in which imipramine and an inert substance were compared (237) showed clear drug superiority, while a second VA study (155), using a slightly lower dose of imipramine (225 mg *vs.* 170 mg) and 1 mg per day of atropine as control, showed few significant differences between the two treatments. In the two other studies, by Uhlenhuth and Park (318) and by Weintraub and Aronson (329), using small doses of atropine as control, the differences between the two treatments were not great. One wonders if atropine in a lower dose may not simulate both the side effects and the main effects of imipramine, especially since many of the actions of imipramine in animals resemble atropine effects. Alternatively, the occurrence of side effects may increase the efficacy of the pill as suggestion and so produce a stronger placebo response. In a recent study, Hare *et al.* (133) used a dextroamphetamine-amobarbital combination pill as control medication and found that patients treated with

imipramine showed significantly less agitation and more weight gain than did the control group. Here one wonders if the difference may not be attributed as much to the anorexic and motor stimulant effects of the dextroamphetamine as to the therapeutic prowess of imipramine.

C. Selected aspects of clinical actions

1. Dose and route of administration. In receiving the clinical literature, it is difficult to avoid the conclusion that insufficient attention is being paid to the major parameters of drug treatment: dose, route of administration, and duration of treatment. Dose is a central concept in pharmacology, but one to which the investigators of one of its branches, clinical psychopharmacology, have not given sufficient attention. A general pharmacologist reviewing the clinical papers would find most of them of limited usefulness because findings are almost always expressed in terms of fixed doses rather than in terms of dose-response curves.

In designing clinical trials of drugs, decisions on dose schedules are often a major problem. Most dose-response studies in animals involve single doses and acute responses. In contrast, when a drug is used clinically, chronic administration at varying dose levels is almost always necessary. There is considerable disagreement on the proper research procedures, especially between fixed dose schedules and variable dose schedules. Should one use standard daily dosages for the whole patient group or should the individual's doses be adjusted for body weight? Should one use a somatic end point for dose regulation, *e.g.*, the appearance of hypotension or other autonomic effects with imipramine, or the appearance of extrapyramidal signs in treatment with the phenothiazines? With the MAO inhibitors, is it possible to utilize biochemical measures, such as determinations of urinary tryptamine? Considerable methodologic research comparing alternative dose schedules is necessary before ultimate agreement can be reached on dose schedules and on the use of somatic criteria. At this point it is hard to foresee the specific outcome of such research.

There seems little evidence that parenteral administration offers advantages over oral use and most clinicians use the oral route exclusively. There is general consensus on a dose range of 75 mg to 125 mg per day for outpatients and 100 mg to 200 mg per day for hospitalized patients. In recent months, a number of suggestions have been made that the failure of many studies to demonstrate the efficacy of imipramine over placebo may be due to the fact that the dose usually used, 100 to 200 mg per day, is inadequate. Some researchers have argued that, if doses were pushed to 200 to 300 mg of imipramine, more definitive therapeutic actions would become apparent (95, 335). One report (335) noted that after a negative small controlled study at about 150 to 200 mg a day, a second similar small study with higher doses (240 mg a day or more) did show imipramine to be effective. Many investigators feel, however, that pushing the dose over 200 mg is seldom accompanied by increased symptomatic improvement (101). Over 400 mg/day generally produces adverse effects, particularly postural hypotension, insomnia and restlessness, which preclude routine clinical use (151). More systematic investigations of dose regimens seem strongly indicated.

2. Onset and speed of clinical actions. Imipramine is widely believed to require one to three weeks of administration before clinical efficacy appears. Although data concerning the duration of depressive illness under placebo are less often reported, depression is generally a self-limited illness; the longer the study, the more likely it is that patients will get well spontaneously or respond to the combination of placebo and the psychotherapeutic or environmental influences to which they are concomitantly being exposed. Parenthetically, it must be noted that there is no published study directly comparing the ability of placebo to reduce symptoms in depressed patients to a greater extent than occurs with hospitalization alone or psychotherapy or nonspecific therapies.

Although studies have shown significant differences between imipramine and control medication after treatment periods ranging from two to ten weeks, in three studies, those by Uhlenhuth and Park, Robin and Langley, and Overall *et al.* (237, 265, 318), significant differences were found between the treatments at an early rating period (at two or three weeks) but there were no significant differences at one month (in two instances) or at three months (in one instance). In the first two studies it would appear that the control group began to catch up with the imipramine group, while in the study reported by Overall *et al.* the clear treatment successes had left the hospital and the clear treatment failures had been dropped from the study by three months, leaving only the more chronic patients showing equivocal responses.

3. Duration of treatment. Because of the tendency of many depressions to recur, clinicians have explored the value of long-term drug treatment in the hope of promoting symptomatic remission and social adjustment and preventing rehospitalization. A few follow-up studies have now been reported which suggest the value of treatment up to six months or one year, but more extensive controlled studies are required (158, 177, 280, 339).

4. Somatic effects. The autonomic and cardiovascular effects usually seen are understood in terms of the known atropine-like actions of the tricyclic antidepressants. Yet increased sweating is frequently reported and is often quite annoying to patients. Clinical studies on EEG and evoked potentials have been reported (92, 118, 117, 282). Evidence of changes in fluid distribution and in various electrolytes, particularly calcium, sodium and potassium, are of considerable interest in view of the possible relations of these variables to electrophysiological abnormalities in depressed patients (48, 97, 281). Depressed patients have very high urinary and plasma levels of adrenal cortical hormones and recent work indicates that effective drug therapy tends to reduce these to normal (113, 136). However, these are probably nonspecific effects occurring also with ECT and other treatments, as reviewed by Durrell and Schildkraut (83).

5. Psychodynamic effects. Psychoanalytic concepts of depression have wide acceptance and utility in clinical psychiatry (126, 224). Several attempts have been made to apply these concepts to the understanding of drug actions (24, 235, 273). Particular emphasis has been placed on the vicissitudes of aggressive drives (24) and increases in hostility and irritability have been documented in normal subjects and in general medical patients receiving imipramine (75, 166).

6. Schizophrenic disorders. Although a number of early investigators reported beneficial clinical effects in schizophrenic patients treated with imipramine, it is now generally felt that the increased activity and social participation observed were due to psychomotor stimulation and were not accompanied by improvement in other areas of psychopathology (88). For example, patients might simultaneously be more socially active and outgoing while also hallucinating and more disorganized in their speech. There is now good evidence that schizophrenics with depression do less well than do other depressed patients on imipramine (111, 125). Moreover, the presence of paranoid features in depressed patients is significantly associated with a poor outcome on imipramine (104, 161, 248, 338). In fact, ability of imipramine and some other antidepressants to cause an increase in disturbed behavior in chronic schizophrenics has provided a screening method, the negative response of these chronic nondepressed patients being used to predict a positive effect of the same compounds in primarily depressed patients (91).

7. Anxiety states and phobic reactions. Another clinical effect of imipramine (19, 118, 184), which it may share with some MAO inhibitors, is an ability to relieve symptoms in a group of nondepressed patients who suffer from recurrent severe anxiety episodes and in whom severe dependency needs and phobic anxiety are manifested between episodes. This syndrome appears to be unresponsive to "tranquilizers," including phenothiazines, chlordiazepoxide, meprobamate, etc., but does respond to imipramine.

8. Uses in other clinical disorders. Although the overwhelming proportion of clinical reports has dealt with depression and the related psychiatric disorders referred to, other disorders have been observed to respond to antidepressant drugs. Controlled studies have been reported of beneficial effects of imipramine in patients with allergy (117) and parkinsonism (219). Its possible usefulness in enuresis has been a subject of controversy (211, 212). Interesting effects have been observed in patients with functional complaints, psychosomatic disorders and hypochondriacal patterns; this observation confirms previous reports of a high frequency of depression among patients seen in general medical settings (166, 207).

D. Factors influencing clinical response

Critical assessment of the clinical literature is hampered because investigators often describe their groups of depressed patients in idosyncratic or overly general descriptive terms. In different settings, depression is described as a symptom, as one of the series of syndromes, or as a specific disease. The range of patients included in the given clinical investigation varies substantially from study to study. For example, some studies divide their patients into "neurotic depressions" and "psychotic depressions"; others into "reactive" and "endogenous," and still others into "retarded" and "agitated." Since many of these modifying adjectives are descriptive terms that define a patient group in only one of several possible dimensions, it is often difficult to compare results from one study to another. Some studies are made in a clearly restricted patient population, as, for example, women under the age of 40 in studies of Wittenborn *et al.* (338, 340). At the other

extreme are studies which include all patients entering a hospital who manifest any depressive symptom, irrespective of the psychiatric or medical condition with which it may be associated (127). Thus, these studies may include patients with severe but normal grief reactions, psychopathic individuals made unhappy by limitations on their activities, patients with the classical symptoms of severe retardation, patients with psychotic involutional depressions, and acutely schizophrenic patients who show depressive features. Such a heterogeneous group of patients should not be expected to show a uniform or systematic response to any type of treatment. Some form of classification is obviously necessary; however, as will be discussed below, there is lack of consensus among psychiatric investigators on the criteria upon which to subdivide patients.

1. Problems in separating schizophrenia from depression. Most teaching of medical students and residents has followed the formula: in the presence of schizophrenic, paranoid, or manic psychoses, prescribe phenothiazines; in the presence of depression, prescribe imipramine or a MAO inhibitor. This formula follows the classic Bleulerian-Kraepelinian division of the psychoses into the disorders of affect and the disorders of thinking (101, 165, 204).

As will be discussed below, until very recently most American and British discussions of the drug treatment of depression did not emphasize any direct antidepressant actions of the phenothiazines. Most authorities regarded the use of phenothiazines in depression as secondary, usually being reserved for patients whose depression is characterized by anxiety, agitation, insomnia, or paranoid delusions. However, in recent months two well controlled studies have offered persuasive evidence for the direct antidepressant effects of the phenothiazines. Overall and Hollister and their associates (236) have presented data that one of the phenothiazines, thioridazine (Mellaril), seems to be about as effective as imipramine in the treatment of depression. Similarly, Fink *et al.* (94) have presented evidence that the combination of chlorpromazine and an antiparkinsonian drug is comparable in efficacy to imipramine in selected hospitalized depressed patients. (As yet, few adequate trials of combined phenothiazine and imipramine-like drugs have been conducted. Nor do there exist carefully designed comparisons of phenothiazines with MAO inhibitors.)

It is of interest, however, that the converse does not hold true. There is little evidence for the utility of imipramine or amitriptyline as a primary treatment of schizophrenic or paranoid states. On the contrary, there seems to be reasonably good evidence that approximately 25% of depressed schizophrenic or schizoaffective patients treated with imipramine or MAO inhibitors will have an aggravation of their psychoses (111, 125). Moreover, the presence of paranoid features is correlated with unfavorable response to imipramine (248, 338). This whole area is in considerable confusion. The forthcoming NIMH-PSC study of drug treatment in depression, in which imipramine will be compared with placebo and with chlorpromazine in a large sample of patients, may help clarify these issues.

2. Classification within the depressions and differential drug responses. Lacking etiological criteria for diagnosis, the investigator faces another major problem: to what extent should the population of depressed patients under examination be

subdivided? Numerous classifications of depression exist. Some studies distinguished between "neurotic depression" and "psychotic depression" (237); others between "agitated depression" and "retarded depression" (197, 198); others distinguished involutional groups from the premenopausal group (340). The work of Greenblatt *et al.* in the large Massachusetts collaborative study indicates that there are strong interactions between factors such as age and type of depression in influencing response to drugs (127). Patients under 40 and those with predominantly neurotic depressions seem to have a very high placebo response rate, whereas patients with schizo-affective components seem to do poorly with imipramine and MAO inhibitors (124, 125).

A few interesting recent studies utilize the separation of depression into endogenous and reactive types in understanding drug effects (178, 180). Some data suggest that response to imipramine is highly correlated with the criteria of "endogenous depression" formulated by many British authors (7, 180). At the same time, Sargant and his associates, West and Dally, also in Britain, have proposed that patients with so-called "atypical depression" or "hysterical depression" are more responsive to MAO inhibitors (69, 334). However, these patients seem similar to the anxious and phobic groups reported by Ayd (18), Goldman (118), and Klein (184) as responding favorably to imipramine.

Phenomenological differentiations of depressed patients have been developed, using symptom patterns and clusters derived by multivariate statistical techniques. Grinker *et al.* (126), Friedman *et al.* (103), Hamilton (130) and Wittenborn *et al.* (336, 337) have published promising findings. It is highly likely that there are significant drug-symptom interactions (185, 338), but exactly how they are related to differential responses to antidepressant drugs remains for future investigation to demonstrate.

3. Hospitalization status. If one divides the imipramine-placebo controlled clinical trials into three groups, one finds that in outpatient studies 71 % of the 213 imipramine-treated patients were judged improved, while on placebo only 21 % of the 186 patients were improved. In inpatient studies of newly hospitalized depressions, 62 % of the 269 imipramine-treated patients were judged improved while 46 % of the 199 placebo-treated patients were judged improved. In chronically hospitalized, depressed patients, 60 % of the 58 imipramine-treated patients were judged improved while only 16 % of the 64 placebo-treated patients were so rated (see Tables 2, 3). Imipramine causes significantly more improvement than placebo in each of the three patient groups. The major differences here lie not in the response rate to imipramine but in the improvement on placebo. The relatively high rate of placebo response in hospitalized acute depressions may attest to the positive effect of hospital milieu and environmental change on acutely depressed patients. Otherwise it is hard to understand why acute depressions treated on an outpatient basis should do so much less well on placebo, especially since trend runs counter to the usual tendency for outpatient groups to show higher placebo response rates than hospitalized patients. Considerably more work in this area is obviously needed.

4. Validity and sensitivity of assessment measures. Although the reliability of

psychiatric diagnoses is often questioned, most, but not all, clinical researchers are now agreed that reliable and valid quantitative measure of clinical outcome is feasible and applicable in psychopharmacological investigation (10, 208, 209, 223, 336, 337). As recently as 1959, there was considerable doubt about the reliability and sensitivity of rating scales and other techniques (61). Since then, the consensus has shifted markedly. Most workers in the field are reasonably satisfied that it is possible to develop reliable and sensitive indicators of clinical improvement. For example, in studying hospitalized patients, especially severely depressed or schizophrenic patients, well validated scales, particularly by Lorr (208, 209), Wittenborn (336, 337), Hamilton (130), and others (213, 326) are widely used. Instruments for nursing observations and for patients' self-ratings also have been developed (30, 137, 326).

In the 23 controlled studies outlined in Tables 2a, 2b, and 3, a number of assessment measures were used. Statistically significant differences between the imipramine and control treatment were found most frequently on global ratings of improvement (11 out of 12 studies using this approach). Total morbidity scores (usually the arithmetic sum of ratings of the severity of a number of symptoms or signs) on clinical rating instruments covering a variety of aspects of depression demonstrated differences in three (104, 318, 335) out of the six studies (125, 151, 271) where this approach was used. One study showed imipramine-placebo differences only on the Minnesota Multiphasic Personality Inventory (137, 271), while seven studies (94, 133, 154, 237, 256, 318, 340) showed imipramine-placebo differences on some individual items of psychopathology or on factor scores measuring aspects of psychopathology. Only two studies, by Friedman *et al.* (104) and by Höhn *et al.* (151), failed to find major differences on measures of this sort. Drug-placebo differences were revealed by global estimates of degree of depression and by ratings of specific symptoms like anxiety, insomnia, weight gain, and guilt. Hamilton's rating scale, Lorr's Inpatient Multidimensional Psychiatric Scale, and the Wittenborn Psychiatric Scale were sensitive to differences in most studies in which they were employed.

Some differences based on the nature of the observer were noted. In one study (133), only the more senior psychiatrists' ratings discriminated between the treatments. In another (329), only the ratings of the individual residents treating the patients discriminated, while ratings of the senior resident on the ward did not. Generally, psychiatrists' ratings discriminated better than nurses' ratings.

5. Personality and attitudinal variables. In recent years, investigators have emphasized the importance of the social milieu, the attitudes of the physician and of patients, and the social background of the patients (131, 260, 285, 318). For example, Rickels (260) has shown that lower class, depressed outpatients referred from a medical to a psychiatric clinic do better on the combination of meprobamate-benzetyzine than on imipramine, while middle class, depressed patients, generally self-referred, attending a psychiatric clinic at a university hospital do better on imipramine. The clinical difference may be due to differential toleration of side effects. The medical clinic patients disliked the autonomic side effects of imipramine and liked the drowsiness induced by the combination,

while the psychiatric clinic patients disliked the drowsiness of the combination while accepting imipramine's side effects as appropriate in an active drug. Each was effective more frequently than placebo in the clinic group which tolerated it best. The interaction of drug effects with variables such as social background, personality type and treatment milieu is a very complex research problem and adequate discussion is beyond the scope of this paper. Indirect support for the importance of social factors is derived from animal experiments on the effect of group size and related variables on the toxicity of amphetamine.

IV. COMPARATIVE STUDIES

A. Imipramine vs. electroconvulsive therapy

In assessing the efficacy of antidepressant drugs it is important to remember the prior existence of an effective nondrug treatment for severe depression, namely electroconvulsive therapy (ECT) (165). Usually, this treatment is administered only by psychiatrists in an hospital setting. In contrast, most depressed patients are treated with drugs on an outpatient basis by nonpsychiatric physicians.

No study claims greater efficacy for imipramine than for electroconvulsive therapy. In the three studies directly comparing the treatments, two show ECT to be considerably superior (125, 264). These trials included only a minority of patients with neurotic or reactive depressions. The third study, by Wittenborn *et al.* (340), found imipramine to be comparable to ECT in a group of depressed women aged 20 to 45 (premenopausal), a group with predominantly neurotic depressions. He may have shown, indirectly, something which clinicians have asserted in other contexts, that ECT is not a desirable treatment for "neurotic" depressions. It is hard to define patient types who would clearly do better on imipramine than on ECT. However, a few studies (28, 177) have shown that imipramine is effective as maintenance therapy in preventing recurrences. This may suggest an advantage of drug over ECT in long-term therapy.

There is disagreement whether ECT is more rapidly acting than drug therapy, and, therefore, whether or not ECT is the treatment of choice in severe depressions in which suicide is a real danger (71, 150, 163, 230, 335). To resolve these issues, controlled data which quantify the rate of change of improvement are necessary, to find what might be called the "kinetics" or treatment response.

B. Imipramine vs. monoamine oxidase (MAO) inhibitors

The only MAO inhibitors directly compared with imipramine to any extent in controlled studies are isocarboxazid, phenelzine, and tranylcypromine. Only the imipramine-phenelzine studies, six in number (5, 125, 138, 176, 202, 218), permit any comparison of crude improvement rates. Here, 138 out of 196 patients improved on imipramine (71 %) as against 101 out of 164 patients on phenelzine (62 %). This difference is statistically significant only at the 0.10 level and clearly not one to be picked up easily by a practicing physician. Martin's study (218), the only study in outpatients, showed a significant difference favoring imipramine. The other studies showed no clear difference between the drugs.

The results of studies by Greenblatt *et al.* (124) and Overall *et al.* (236) comparing imipramine with isocarboxazid favored imipramine. A third study by Rothman (268) slightly favored isocarboxazid. Two studies have shown tranylcypromine to be comparable in efficacy to imipramine. On the other hand, the evidence favoring the clinical superiority of the MAO inhibitors over placebo is equivocal (60), although selected subgroups of patients may be highly responsive to these drugs (239).

C. Imipramine vs. amitriptyline

Amitriptyline is the only other tricyclic antidepressant which has been extensively studied. In five controlled clinical trials comparing it to placebo, four, those by Browne *et al.* (49), Garry and Leonard (110), Master (220) and Skarbek (292), reported the superiority of amitriptyline over placebo. Two of these positive studies, by Garry and Leonard (110) and by Skarbek (292), were carried out in chronically hospitalized depressed patients, a group in which comparable studies of imipramine had shown generally a less striking drug effect. The one negative study, by Hollister *et al.* (155), compared imipramine and amitriptyline with 1 mg of atropine as the control medication. Both drugs were significantly better than atropine on only one of nine measures examined, this one being the conceptual disorganization scale of the Inpatient Multidimensional Psychiatric Scale, presumably a measure of thinking disorder, rather than of depression *per se*. In measures of depression, amitriptyline was superior to imipramine in the more severely depressed patients on the anxious-intropunitive scale, a measure of guilt and depression. Unfortunately, this study utilized no global outcome measure.

A detailed and thoroughly analyzed study of depressed female inpatients by Hordern *et al.* (51, 160, 161) concluded that amitriptyline is slightly but significantly superior to imipramine on a number of criteria. This superiority was particularly striking in the more severely depressed and older women in the study. The differences between the two drugs showed most clearly on such symptoms as insomnia and agitation as well as on depression itself. In addition, patients with delusional symptoms, who generally do poorly on imipramine, did less badly on amitriptyline. Hoenig and Visram's study (149) also showed amitriptyline to be superior to imipramine and found that patients begin to show a therapeutic effect from amitriptyline slightly earlier, 9 *vs.* 10.2 days on the average. Snow and Rickels' study (295), comparing the two drugs, also showed amitriptyline to be superior, but here the dose of imipramine used was only half that of amitriptyline, whereas most clinicians regard the effective dosages of the two drugs to be about the same. Amitriptyline has more hypnotic effect than imipramine and is less likely to increase agitation or delusional thinking. It may be faster acting than imipramine.

In general then, amitriptyline may be slightly more effective than imipramine, particularly in severe or chronic depressions.

D. Imipramine vs. desipramine

There has been considerable interest in desipramine because it is a metabolite of imipramine and acts more rapidly than imipramine in many animals (43). It has been suggested that desipramine is indeed the active principle underlying

imipramine's efficacy (222). Clinical trials have only partially confirmed the pharmacological predictions of increased potency and rapid onset of clinical action (25, 28, 108, 154, 215, 216, 231, 244). In an attempt to test whether or not desipramine is the active metabolite of imipramine, Yates *et al.* (341) found that plasma levels accounted for only a small proportion of imipramine and plasma concentrations seemed to be inversely proportional to body weight. There appears to be no correlation between the onset of clinical effect and plasma levels of desipramine or platelet levels of 5-HT.

A study by Hollister *et al.* (154), using techniques which had discriminated between imipramine and placebo in an earlier study, found desipramine to be slightly less effective than inert placebo after three weeks of therapy. However, the dose employed, 100 mg of desipramine, is below the currently recommended daily dose. One controlled clinical trial directly comparing the imipramine and desipramine (266) found no difference between them after either one or three weeks of treatment. Unfortunately, all the patients in this study also received 150 mg of thioridazine per day, and this medication may well have reduced any real difference between the treatments. A further study by Wilson *et al.* (335) also found no differences in efficacy or speed of onset of clinical effects between imipramine and desipramine.

E. The tricyclic antidepressants vs. the phenothiazines

There is a general assumption in European psychiatry that the drugs under consideration exhibit a spectrum of activity. Drugs like chlorpromazine are considered principally antischizophrenic and those like imipramine are considered principally antidepressant, while drugs like thioridazine, levomepromazine, amitriptyline, and chlorprothixene, are thought to exhibit varying amounts of both properties. These clinical similarities parallel the animal pharmacology of these compounds. The European view may indeed be true in selected areas, although evidence from controlled studies is at present only suggestive. A small study by Denber and Bird (72) showed a combination of chlorpromazine with an antiparkinsonian agent to improve chronic depressions while chlorpromazine alone did not. Fink *et al.* (94) have found both imipramine and chlorpromazine-procyclidine combination to be more effective than placebo in hospitalized patients having depressions. He found the chlorpromazine-antiparkinsonian combination most effective in reducing agitation and tension, while imipramine was more "alerting." Since both imipramine and amitriptyline resemble chlorpromazine in animals but have some effects like those of antiparkinsonian drugs, the drug combination noted above may mean that chlorpromazine is closer in its clinical pharmacology to the antidepressants than has been thought.

The recently published study by Overall *et al.* (236) showed thioridazine to be superior to imipramine, in both depressed and schizophrenic patients admitted to several collaborating VA hospitals. A subsequent re-analysis of these data has considerably clarified their general finding. If the depressed patients are stratified into "anxious" depressions, "hostile" depressions and "retarded" depressions by means of special psychometric techniques, imipramine is superior to thioridazine in the "retarded" depressions, while thioridazine is superior to imipramine in the

"anxious" depressions, and they are equally effective in the "hostile" depressions. The overall superiority of thioridazine resulted from the relative preponderance of anxious over retarded depressions in the total sample. The above findings suggest that phenothiazines possess efficacy in treating selected components of depressions. The differences between the two groups of drugs are most striking in their effects in schizophrenic patients, in whom the phenothiazines are quite effective by reducing psychotic psychopathology while imipramine and some of the other tricyclic antidepressants appear to increase schizophrenic symptomatology.

V. ADVERSE EFFECTS

General problems of adverse effects and complications associated with psychopharmacologic agents have been reviewed by Hollister (153) and others (15, 61, 62, 165). In evaluating reports of adverse effects of antidepressant drugs, baseline assessments and control group comparisons are essential. Hordern *et al.* (161) and Busfield *et al.* (52) have stressed a major source of confusion in the clinical literature on drug evaluation in depression: many of the symptoms noted as side effects are also spontaneously occurring physical complaints and symptoms associated with depression. Careful reporting of the frequency of such complaints prior to drug therapy and the use of control groups are necessary to separate drug effects from the many somatic symptoms associated with depression.

A. Autonomic effects and cardiovascular problems

Autonomic effects of imipramine and amitriptyline are generally not severe but are often a considerable nuisance to both doctor and patient (53). Most autonomic side effects are manifestations of the known actions of the drugs as seen in animals. They can usually be controlled by adjustment of dosage and tend to be less troublesome after two to three weeks of therapy. This is true of the more common side effects: dry mouth, increased sweating, difficulties with visual accommodation, and constipation. Urinary retention may be a problem in older patients (169).

Cardiovascular complications may be more serious, particularly with imipramine (228). Postural hypotension and tachycardia are frequently noted (about 5% of all cases). Both are usually mild and without ill effect in most patients (159). However, these effects have been implicated in cases of serious cardiovascular incidents in patients receiving imipramine; cases of coronary thrombosis (100, 217, 294), congestive heart failure (217, 273, 294), and pulmonary emboli (198, 217) have been described. Many patients who experienced difficulties were elderly and had pre-existing cardiovascular disease, in addition to the stress often imposed on the cardiovascular system by the depressive state itself. The need for caution, particularly in the elderly or those with existing cardiovascular disease, seems well founded until safety limits are more firmly established.

B. The brain and behavioral toxicity

Convulsions (38, 88, 100, 201, 284) are more likely to occur in patients with a history of epilepsy or with previous EEG abnormalities (179) but also occur in the absence of these.

A persistent tremor, fine, rapid and more marked in the upper extremities, has been described in as many as 10 % of patients treated with imipramine. It appears to be unlike the extrapyramidal type of tremor seen in patients taking phenothiazine derivatives. There are two reports of a gross disturbance in motor function occurring in elderly patients (84, 98) with resulting serious falls. Insomnia is common in the early period of treatment with imipramine, and also with protriptyline, but it is transitory and responds well to nighttime sedation. Dizziness, too, is transitory and is perhaps related to blood pressure changes.

A more serious adverse behavioral effect is the occasional occurrence of hypomanic or schizophrenic excitements (107, 205, 263, 279). The manifest symptoms, including delusions, hallucinations, overactivity, and confusion, usually subside within 48 hours after discontinuance of the drug, but have been reported to persist up to eight weeks, even with phenothiazine administration, the preferred treatment of this complication (28, 39, 174, 263, 279).

C. Allergy and hypersensitivity

When allergic skin reactions occur with imipramine they are usually noted early in therapy and often subside with reduced dosage. Photosensitivity seems to be less of a problem with imipramine than with chlorpromazine.

1. Jaundice and liver damage. Jaundice has been reported in less than 0.5 % to 1 % of the cases treated with imipramine. In most instances there was some evidence of possible liver disease of other etiology, yet the jaundice in all cases cleared rapidly after cessation of treatment. No marked or consistent changes have appeared in routine liver studies. The hepatitis observed is obstructive in type and seldom involves parenchymal tissue. In most respects it resembles the very mild forms of jaundice seen with the phenothiazines. The onset is usually within the first few months.

2. Agranulocytosis. Agranulocytosis is a rare but serious complication of the use of imipramine. Approximately twelve cases have been reported, including three fatalities (20, 37, 38, 59, 68, 82, 121, 139, 226, 267). Both leukocytosis and leukopenia (205) have been noted by other authors as well as a low grade eosinophilia (36, 198, 205), but no other consistent changes in blood picture have been reported. Like the blood dyscrasias with phenothiazine treatment, the agranulocytosis seen with imipramine is considered a form of allergic hypersensitivity. It usually appears after the first month and within the first four months. Elderly women seem the most frequent and serious cases (21). The incidence of agranulocytosis seems lower in imipramine-treated patients than in patients treated with chlorpromazine.

D. Incompatibility of combination with monoamine oxidase inhibitors

It is dangerous to combine a MAO inhibitor with tricyclic antidepressants or to change from one type of drug to the other type without waiting at least a week (20). Cases have been reported in which severe dizziness, tremor, restlessness, hallucinations, profuse sweating, vascular collapse, and extreme hyperpyrexia have resulted from such combinations (20, 41). These complications are less likely to occur in patients initially treated with a tricyclic compound who are subse-

quently changed to MAO inhibitors than in those who receive the drugs in the reverse sequence. These reactions have been investigated in animal experiments and are understandable in terms of known ability of these drugs to potentiate norepinephrine and other amines (147, 148) (Section II E and II G).

E. Other effects

Attempted suicide, in patients who ingested up to 3000 mg of imipramine (38, 135, 199), has been managed by symptomatic treatment. The clinical picture was characterized by stupor, ataxia, choreiform movements and grand mal convulsions. Recovery was complete in two to three days.

Although attempted suicide is not strictly a complication of therapy, it is a real possibility in a depressed patient treated with imipramine. Severely suicidally depressed patients may not be able to tolerate their discomfort for the week or two necessary for the full effect of the drug to appear. The increase in volitional activity before an affective response has occurred may be responsible for attempted suicide. A number of authors have discussed this possibility and have cautioned practitioners against the indiscriminate use of the drug because of the possibility of suicide in such patients.

Lactation has been reported (186). The possibility of fetal damage when imipramine is taken by pregnant women has been suggested (262).

VI. SUMMARY AND CONCLUSIONS

Our review of the studies of clinical efficacy of the tricyclic compounds in the treatment of depression supports the general view that imipramine and amitriptyline are more effective than placebo, and that amitriptyline may even be a little more effective than imipramine. The controlled data show a reasonable consistency. Moreover, this review confirms an impression that the authors have gained from other studies that clinical ratings of general improvement and of symptomatic changes are a good deal more useful for detection of drug-placebo differences than has often been assumed.

These heterogeneous reports give few clear criteria, however, of what kinds of depressed patients with what kinds of symptoms are particularly responsive to these drugs. An equally important unanswered question concerns the kinds of depressed patients who respond well to placebo or nonpharmacologic therapies. Imprecision or lack of general agreement on meaningful subgroups among depressions certainly hinders the interpretation of pooled data. For a condition as variable as depression, the sizes of patient samples so far studied appear woefully small. To make progress in this area, larger studies with clearly defined patient groups will be needed. More attention also will have to be given to nondrug factors, including those attendant to the administration of placebo, that influence the therapeutic outcome in depression. There is some evidence that depressed patients are affected by the attitudes of their doctors toward these drugs (285) and some evidence that the patient's expectations influence his responses to placebo (157).

Another particularly fruitful area for further research is that of followup and

maintenance therapy. There is already suggestive evidence that imipramine has unusual virtues as a maintenance therapy and that patients receiving even a short period of drug treatment show better adjustment a year later than do patients treated with control (158, 177, 339).

These agents are reasonably safe if used with care. There is no good evidence that imipramine is significantly more dangerous than ECT. It is probably less dangerous than iproniazid if it is properly used, that is, if the dosage is watched, and its side effects are properly managed either by reduction in dosage or other corrective medication.

Ideally, to understand the mode of clinical action of any therapeutic agent requires knowledge in four areas: 1) objective criteria to identify patients with a specific clinical feature, *i.e.*, anemia, jaundice, depression, anxiety, etc. (this requires knowledge of the range and limits of the phenomena within the normal population); 2) knowledge of etiology on the basis of which groups of patients with a given clinical manifestation can be significantly classified in meaningful groups; 3) understanding both the pathogenesis (*i.e.*, the sequences of events leading to formation of symptoms) and the pathologic physiology and psychopathology of the disease states; and 4) knowledge of the actions of a drug which clarifies how the treatment interrupts the pathogenetic sequence that results in symptom formation or alters the pathologic physiology characteristic of the disease state. This ideal is seldom realized even in the fields of medicine other than psychiatry. In studying the pharmacotherapy of depression, we are hampered by lack of knowledge in all areas. The range of depressive emotional manifestations—in the normal population or secondary to life stresses and medical illness—is undoubtedly wide. Quantitative criteria for determining pathologic depressive reactions are limited. Within the group of depressions, few etiologic principles have been substantiated and little agreement exists on subgroups. Consequently, differential drug responses are not clearly understood. Most significantly for understanding modes of drug actions, we have little knowledge of the altered psychophysiology of depression. It is encouraging that some promising leads are being developed (83, 281).

Nevertheless, the advent of effective psychopharmacologic treatments of depression has provided considerable impetus to basic laboratory research and clinical investigations and a number of new techniques have yielded interesting findings. Among the various hypotheses, most attention has been focused on the relationship of imipramine's actions to effects on central adrenergic mechanisms, probably in hypothalamic and other diencephalic regions. In this respect there appears to be some convergence of data in a number of areas: potentiation of the peripheral actions of norepinephrine, alteration of the uptake and storage of amines, clinical effects on urinary excretion of catecholamine metabolites, and behavioral stimulation. These findings are compatible with the hypothesis that depression is associated with a relative deficiency of catecholamines in selected subcortical regions of the brain and that some depressed patients, like animals receiving reserpine, may have released intracellularly deaminated endogenous norepinephrine to excess, so that less of this amine is available for release in

active form. These results, moreover, suggest that a possible common mode of action of monoamine oxidase inhibitors and the imipramine class of antidepressant drugs may be to increase the active catecholamines, particularly norepinephrine, available for functional extracellular release (188, 277). Attractive as these hypotheses may be, it is important to recognize their limitations. There is no clear evidence of alterations of amine metabolism in depressed patients. The role of cholinergic mechanisms remains unclear as does the possible relationship to indoleamine metabolism (1, 2, 56, 333). Conceptually, considerably more sophistication on regional brain drug effects seems to be evolving, and many widely accepted clinical concepts are undergoing reappraisal and empirical validation. Interesting research on these and related hypotheses are underway and the prospects are that many of these issues will be partially clarified within the next five years.

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