HUMAN PHARMACOLOGY OF ANTIPSYCHOTIC AND ANTIDEPRESSANT DRUGS[1]

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Drugs used to treat patients with schizophrenic or depressive reactions are unusual in two respects: (*a*) Neither clinical application was predicted initially on the basis of pharmacological effects in animals, and (*b*) animal models for evaluating specifically the antipsychotic and antidepressant actions of drugs remain relatively inadequate. It is essential, therefore, to pay particular attention to the actions of these drugs in man. Most knowledge of their effects has been gained in the context of their therapeutic use; pharmacological studies in normal humans have contributed relatively little relevant information.

At least seven chemical classes of antipsychotic drugs ameliorate the symptoms of schizophrenic reactions: phenothiazine derivatives, Rauwolfia alkaloids, butyrophenones, thioxanthene derivatives, benzoquinolizines, phenylpiperazines, and a new class of indolic derivatives (see Fig. 1). The phenothiazines are the most numerous, widely used, and widely studied antipsychotics. Although distinct quantitative pharmacological differences among the various phenothiazines are evident, no major qualitative difference has been established. Numerous large-scale controlled studies have established the efficacy of these drugs in treating schizophrenia, and the lack of differences in therapeutic effects among them (1–3). In addition to the antipsychotic action, these drugs are generally sedative. Most phenothiazines are potent antiemetics, providing an additional clinical use. An unwanted effect of all classes of antipsychotic drugs is the ability to evoke extrapyramidal syndromes in doses not necessarily directly related to therapeutic efficacy.

Only three classes of antidepressant drugs are currently recognized: tricyclic compounds, such as imipramine; hydrazide monoamine oxidase inhibitors (MAOI), such as isocarboxazide; and non-hydrazide MAOI, such as tranylcypromine (Fig. 2). The first group embraces the most important agents; more evidence exists to support their clinical efficacy than exists for the others (4, 5). Recent clinical studies indicate the possible specificity of the tricyclic compounds for certain classes of depressions (6). They also have other actions including considerable central and peripheral antichol-

[1] The survey of the literature pertaining to this review was concluded in July 1967.

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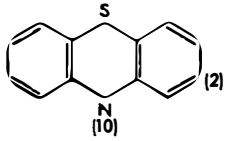
PHENOTHIAZINE DERIVATIVES



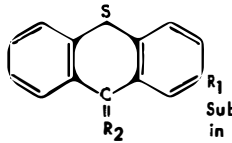
Phenothiazine nucleus

Chlorpromazine (2) Cl (10) CH_2-CH_2-CH_2-N-$(CH_3)_2$

Thioridazine (2) SCH_3 (10) CH_2-CH_2-N-CH_3

Fluphenazine (2) CF_3 (10) CH_2-CH_2-CH_2-N-N-CH_2-CH_2-OH

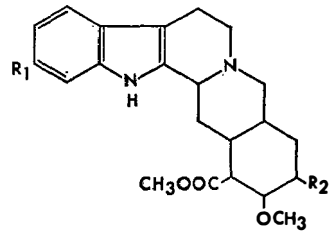
THIOXANTHENE DERIVATIVE

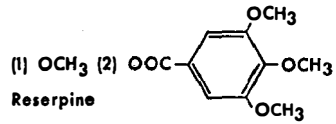


Substituting C for N in the nucleus

Chlorprothixene (1) Cl (2) $CHCH_2CH_2N(CH_3)_2$

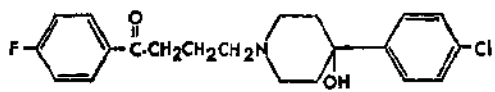
RAUWOLFIA ALKALOIDS





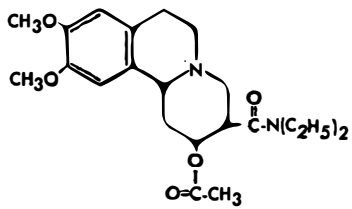
Reserpine

BUTYROPHENONE DERIVATIVES



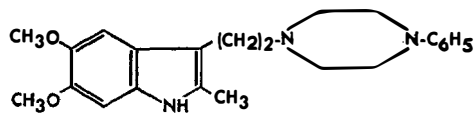
Haloperidol

BENZOQUINOLIZINE DERIVATIVE



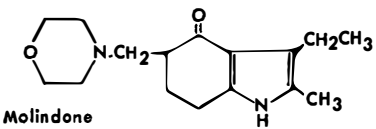
Benzquinamide

PHENYLPIPERAZINE DERIVATIVE



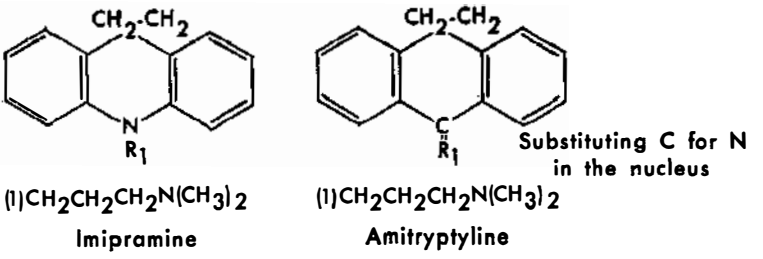
Oxypertine

INDOLE DERIVATIVE

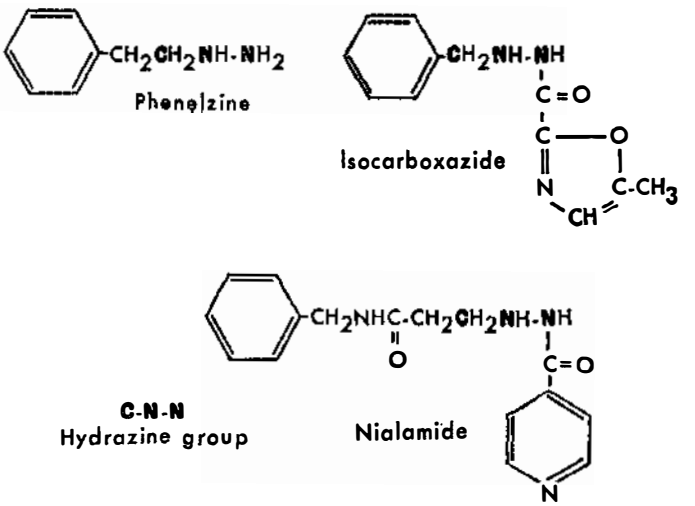


Molindone

TRICYCLIC COMPOUNDS



HYDRAZIDE MONOAMINE OXIDASE INHIBITORS



NON-HYDRAZIDE MAO INHIBITORS

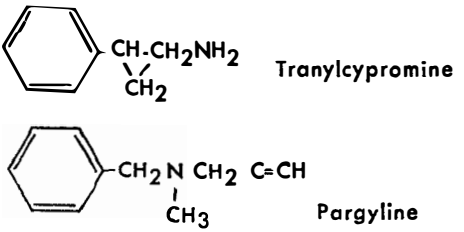


FIG. 2. Chemical classes of antidepressants.

inergic activity; the latter action has not been used clinically. One non-hydrazine MAOI, pargyline, has been employed primarily as an antihypertensive drug.

Psychological Effects

Behavioral actions.—Most antipsychotic drugs are unpleasant to normal individuals; the combination of sleepiness, restlessness, and autonomic effects creating experiences unlike those from more familiar sedatives or hypnotics. Both 50 mg intramuscular doses or 200 mg oral doses of chlorpromazine or thioridazine produced considerable drowsiness in normal subjects after four to six hours. From these and other data, it has been concluded that intramuscular doses are 2.5 to 3 times as potent as the same oral dose. Self-reports indicated that both drugs decreased feelings of friendliness, energy, clarity of thought, or aggression, but had little effect on jitteriness and tended to make subjects slightly more depressed (7). A comparison in normal subjects of chlorpromazine and promethazine in 200 mg oral doses revealed that promethazine was more hypnotic, but little else distinguished the antipsychotic from the antihistaminic phenothiazine. Two piperazinylphenothiazines, perphenazine and trifluoperazine, had different effects at varying doses; either low or high doses produced simultaneous drowsiness and restlessness, and medium doses had a stimulant effect (8). The benzoquinolizine, benzquinamide, was administered in divided doses of 125 mg daily to 20 medical students, most of whom reported more negative than positive effects. The same subjects reported predominantly favorable symptoms of well being and friendliness when treated with a daily dose of 37.5 mg of chlordiazepoxide, and somewhat less favorable effects from placebo (9). Chlorpromazine and thioridazine in 50 mg intramuscular doses were sedative, while benzquinamide in intramuscular doses of 300 mg, or reserpine in doses of 2.5 mg evoked clinical signs of excitement (10). Since the latter drugs are also effective antipsychotic agents, sedation of itself is obviously not correlated with antipsychotic effect.

Antipsychotic drugs may on occasion be "psychotogenic." Four of 17 nonpsychotic tuberculous patients on long-term daily doses of 300 mg of chlorpromazine developed transient psychotic episodes; two manifested by depression, one by psychomotor agitation and one by agitated depression. Pre-existing psychopathology and concurrent use of isoniazid may have contributed to these reactions, which were the first clear psychotic breaks in these patients. Six other patients experienced nervousness, insomnia, and a vague feeling of apprehension while on the drug. After abrupt termination of treatment, four other patients complained of increasing nervousness, restlessness, insomnia, and gastrointestinal symptoms. These mild withdrawal symptoms were managed by resuming chlorpromazine or substituting other sedatives (11).

Normal subjects given 50 mg doses of imipramine or desipramine experienced fatigue. Desipramine appeared to stimulate some patients, al-

though imipramine did not, indicating that desipramine had less sedative effects than the parent drug (12). Following 25 mg doses of each, 13 of 20 normal subjects experienced fatigue from imipramine, 8 of 20, fatigue from desipramine, and 6 of 20 fatigue from placebo (13). However, lack of sedative action cannot be equated with stimulation or antidepressant actions. Clinically, amitriptyline seems to be a better sedative than imipramine, as well as somewhat more effective as an antidepressant.

Apparently the behavioral effects of antipsychotic and antidepressant drugs in normal individuals bear little relationship to therapeutic efficacy. Sedation, in the traditional sense, cannot be equated with antipsychotic effects; nor can stimulation be equated with antidepressant actions. Indeed, the most effective antidepressant drugs, amitriptyline and imipramine, are sedatives in normal persons, and share many pharmacological properties with the phenothiazines.

Intellectual functions.—Single doses of 200 mg of chlorpromazine in normal subjects produced as much impairment of intellect as the same dose of secobarbital. Further comparisons of these two drugs revealed that chlorpromazine decreased performance more in an experimenter-paced test where sustained attention was necessary (the Continuous Performance Test). On self-paced tests (the Digit-Symbol Substitution Test and the Subject-Paced Test), where sustained attention was not necessary, secobarbital decreased performance most, suggesting that chlorpromazine decreases attention span (14). A similar conclusion was reached from a study of 39 disturbed children alternately treated with chlorpromazine or free of drug. Two of seven tests of learning, retention, and performance were impaired by chlorpromazine as compared with placebo. Paired-associate learning became less efficient, especially on later learning trials and among initially slower learning patients. Porteus Maze mental age scores declined. No drug effects were noted on remote or immediate memory (15).

Schizophrenic patients with high IQs could abstract proverbs much better after five weeks of treatment with phenothiazines; the improvement was concomitant with amelioration of schizophrenic symptoms. Patients with low IQs did not show similar changes, but these patients always do poorly on this test (16). In another study, improved performance was noted after treatment with phenothiazines, but the pattern of response differed between drugs (17). The possibility of distinct profiles of psychological effects for different antipsychotic drugs is intriguing, but clinical confirmation of selective actions in psychotic patients is still far from proven.

Somewhat surprisingly, depressed patients treated with nialamide or isocarboxazide for eight weeks declined in performance on each of ten test of intellectual functions, as compared with a similar period of placebo therapy. Even after another eight weeks of placebo treatment, performance had not returned to baseline (18). No mention was made of changes in the clinical state of depression in relation to these changes. In general, most normal subjects treated with these drugs have impaired cognitive functions, while per-

formance of patients improves only with concomitant clinical improvement.

Perceptual tasks.—Size-constancy judgments were no more affected in normals by a 200 mg dose of chlorpromazine than by placebo; in contrast, sleep deprivation produced significant overestimation of size. The latter might be expected when motivation improves, as has been reported in sleep deprivation, but no definite conclusion could be drawn regarding any effect of the drug (19). The apparent eyelevel was reduced by doses of reserpine, tetrabenazine, chlorpromazine, and meprobamate, and raised by LSD-25 and isocarboxazide. Although euphoriant drugs are expected to raise the level, while dysphoriant drugs are expected to reduce it, results were far from conclusive because nialamide, phenobarbital, and dexamphetamine had no effect (20). Thresholds for perception of vibration are increased in schizophrenics and seizure patients as compared with normals. During treatment of schizophrenics with fluphenazine, the threshold became more nearly normal, correlating well with clinical improvement (21). Critical flicker fusion frequency (CFF) was tested in six schizophrenic patients treated with 100 mg of chlorpromazine daily. The drug caused a persistent lowering of the threshold which reached a maximum by the fifth week of treatment (22).

The position of an apparent horizon is elevated in mania and lowered in depression. Single 2 mg oral doses of reserpine lowered the apparent horizon two to three hours later when given to chronic schizophrenic men; similar tests with 100 mg doses of iproniazid produced a non-significant upward shift (20). Ten normal men given a single oral dose of 50 mg amitriptyline showed a significant increase in apparent horizon, which is unusual in view of the sedative action of acute doses of this drug in normals. Six normal subjects treated with 75 mg daily for a month experienced a lesser rise (23). Critical flicker fusion frequency was unchanged one and three hours after single doses of 25 and 50 mg of imipramine or desipramine. Following treatment with 75 mg of imipramine for two weeks, CFF showed a progressive lowering of fusion threshold (13). On the whole, perceptual changes induced by these drugs appear to be nonspecific and of little value in predicting utility or clinical response in patients.

Psychomotor tests.—Oral doses of 100 and 200 mg of chlorpromazine impaired motor coordination more than the same dose of secobarbital in 12 normal volunteers (24). When tests were delayed 14 to 15 hours and subjects were allowed to sleep off the initial acute effects, both doses of chlorpromazine and the larger dose of secobarbital still caused impairment, suggesting a longer effect from the former drug (25). It should be emphasized that single doses of antipsychotic drugs do not reflect ordinary clinical practice where chronic dosage is the rule. When 10 mg of prochlorperazine was given twice daily over a four-week period to normals, no effect was observed on a variety of behavioral tests measuring psychomotor performance, visual acuity, anxiety, or personality variables (26).

A pursuit-meter task under punishment conditions was designed to arouse

anxiety. On doses of 800 mg of meprobamate, continued improvement in performance was noted over successive trials, but after doses of 50 mg of chlorpromazine, 100 mg of pentobarbital or placebo, the task was disrupted. This result was interpreted as indicating a difference between sedative and antianxiety effects of drugs (27). Pursuitrotor performance and tachistoscopic threshold were impaired after chlorpromazine administration in normals, but were somewhat less impaired in schizophrenics; the latter, however, started at a lower initial level of function (28).

The deterioration of speech produced by delayed auditory feedback was decreased by benzquinamide 25 mg orally in normals, and aggravated by alcohol administration (29). Physical performance of trained athletes declined progressively as the dose of the phenylpiperazine oxypertine was increased. Low doses (5 and 10 mg) improved mood, suggesting a stimulating effect, but this was not correlated with the actual physical performance which was maximally impaired after doses of 20 and 40 mg (30).

Twenty normal subjects given 25 and 50 mg doses of imipramine and desipramine one and three hours before testing showed no significant change, as compared with placebo, in reaction time, disjunctive reaction time, tapping speed and coordination. The same was true for a test dose of 50 mg given after two weeks of treatment with 75 mg daily (13).

In general, the more active the drug or the larger the dose, the greater the impairment on psychomotor tests. The crucial clinical question of the effects of such impairment on various potentially hazardous functions, such as driving, during therapeutic administration is still unsettled.

Personality variables in drug responses.—Responses to psychotropic drugs are considerably modified by the personality of the recipients. Although difficult to prove experimentally, the law of initial value seems to apply. The initial level of drive, mood, attention, or activity may influence strongly the direction in which drug effects go. Placebo effects due to expectation, the particular meaning of the drug to the patient, the social status of the patient, and the researcher-subject relationship are fairly well established, although more for the sedatives, antianxiety agents, or stimulants than for antipsychotic or antidepressant drugs. Perhaps more important with the latter two groups are side reactions which may produce a somatopsychic feedback which modifies therapeutic effects.

A number of phenomenologic studies in schizophrenic patients treated with drugs have pointed out some differences based on personality factors. Among a group of patients attending a clinic, it was found that those who tended to deny their illness benefited most by drugs while those who accepted illness were more benefited by milieu (31). Among a group of schizophrenic inpatients, eight patterns of response to drugs were described anecdotally. Of greatest interest was that patients with preponderant somatic complaints, or those with episodes of agitation or anxiety, tended to do poorly (32). I can certainly vouch for the poor reactions of highly somatizing patients to the unusual side reactions of most antipsychotic drugs. Subjects

with contrasting personality features experienced opposite effects from drugs on the task of learning nonsense syllables. A group of eight introverted, intellectual, low-anxiety subjects was impaired, while a group of eight introverted, intellectual, high-anxiety subjects was improved following doses of chlorpromazine, trifluprομazine or placebo, even though the drugs had few overall effects (33). Disruption of performance in extroverted patients was confirmed for two doses of chlorpromazine, as contrasted with two doses of trifluoperazine, a less sedative phenothiazine, and placebo (34). This same difference in personality types applies to reactions to conventional sedative and stimulant drugs (8). Although the relationship between somatotype and personality is still somewhat tenuous, mesomorphic schizophrenic patients seem to respond better to phenothiazines than other somatotypes (35). Body build has also been described as leading to different responses to alcohol.

A number of psychodynamic theories have been proposed to explain differences in reactions of patients to the same drug. One, based on a consideration of characteristic psychological defense mechanisms, hypothesized that patients made worse by drugs such as chlorpromazine or reserpine respond adversely because the drugs limit outlets in the areas of expression of affect, and of libidinal and aggressive energy, defenses which are important for these individuals (36). Libido, also defined as psychic energy or the extent to which one has an impulse to act, has been used in a simplistic fashion. If the patient has too much energy (is highly active), a "tranquilizer" is right for him; if he has too little, an "energizer" is appropriate (37). Similar attempts have been made to explain drug actions on the basis of "ego strength," but even the investigators themselves have difficulty in deciding what this is or how to measure it. Often I have the feeling that the most naive psychoanalytic notions masquerade under cover of obscure language. While it seems reasonable to expect personality factors to be related to responses to drugs, their study by usual measuring techniques has not been very fruitful in predicting drug actions (38).

Physiological Actions

Electroencephalographic studies.—Both single and repeated doses of reserpine, chlorpromazine, and thioridazine produce shifts in the pattern of EEG frequencies, chiefly in the direction of slowing and increased synchronization. At times, the slowing (hypersynchrony) is focal or unilateral and may lead to erroneous diagnostic interpretations (39). Both the frequency and amplitude changes induced by psychotropic drugs are readily apparent on "eyeball-analysis," and confirmed by the more sophisticated electronic techniques of analysis. Other antipsychotic drugs produce similar changes.

Two aspects of EEG amplitude associated with psychoactive drugs, the mean energy content (mean amplitudes of all waves), and the coefficient of variation, have been recently studied. Schizophrenic patients do not differ from normals in mean energy content but have a lower coefficient of varia-

tion (40). Antipsychotic drugs given to schizophrenics did not change the mean energy content but increased the coefficient of variation. These shifts were believed to be correlated with clinical improvement (41).

EEG changes associated with psychotropic drugs appear first in subcortical electrodes, providing the basis for the suggestion that the drugs act predominantly subcortically (42). Chlorpromazine has been found to decrease the latency of rapid eye-movement sleep and to increase precentral fast (18 to 26 cps) activity during sleep and wakefulness. It has been speculated that the drug enhances the effect of the limbic system on cortical activity (43).

The hypersynchrony produced by these drugs may account for their activating effect on the EEG of epileptics, as well as their occasional elicitation of fits in patients who have never had seizures. Since thioridazine and drugs which are much more potent in eliciting extrapyramidal effects produce similar EEG changes, it is unlikely that the EEG reflects changes in the extrapyramidal system. This has been borne out by clinical experience; extrapyramidal syndromes are no more common in patients with EEG changes than in those without.

It is of prime importance to know whether or not EEG changes may be used to evaluate treatment. Conflicting results have been obtained from clinical studies in which behavioral indices were correlated with EEG changes produced by drugs. One of the most systematic of these, a comparison of the phenothiazine, thiopropazate, with the butyrophenone, haloperidol, revealed that although both drugs produced the expected mild slowing of rhythm, no relationship could be seen between such changes and the degree of clinical improvement (44). Desirable as it might be to have a physiological predictor of clinical response as simple to obtain as an EEG, this hope is still not realistic.

Interesting relations between EEG patterns and behavior have been reported for imipramine. In its production of increased theta and decreased alpha activity, the effects are similar to chlorpromazine, but in quantitative studies, the increased delta and decreased fast activity characteristic of chlorpromazine clearly differentiated it from imipramine (45). Single intravenous doses of imipramine produced desynchronization and increased theta rhythms, like the anticholinergic hallucinogens (46).

Both imipramine and amitriptyline evoke seizures and like the phenothiazines, may activate tracings of epileptic patients. Intravenous doses of 30 mg of amitriptyline evoked or enhanced paroxysmal activity in 11 of 20 epileptics. Only nonspecific changes similar to those produced by chlorpromazine and imipramine were noted in 18 of 20 depressed nonepileptic subjects (47). The EEG activation was considered independent of any antidepressant effect. The increased beta activity following thiopental, characteristic for schizophrenics, was aggravated after treatment with imipramine or iproniazid, concomitant with aggravation of the psychotic state (48).

All the antipsychotic drugs, phenothiazines, butyrophenones, and

thioxanthenes, as well as reserpine, produce frequency shifts toward the slow end of the spectrum, while the antidepressants commonly produce desynchronization and increased theta and beta activities. The greatest difference is seen in the minor tranquilizers, however, such as chlordiazepoxide, meprobamate, the barbiturates, and diazepam, which produce increased synchronization and increased beta activity, without the changes in slow frequencies seen with the major tranquilizers. The minor tranquilizers also are often associated with problems of withdrawal and habituation, phenomena rarely seen with the antipsychotic agents.

These differences have led some investigators to propose that the induced EEG changes provide leads regarding clinical utility and a basis for the classification of new psychotropic drugs (49–51). This opinion is largely based on the long-standing hypothesis that drugs which increase EEG synchronization are associated with sedation, while those with a desynchronizing effect have opposite clinical actions (52). While this hypothesis may be true, one must constantly beware of the semantic pitfall of equating sedation with antipsychotic action and stimulation with antidepressant action. In practice, EEG studies have not been very useful, at least in my experience, in managing individual patients because of variability of response of individual patients to drugs.

Endocrine and metabolic effects.—Phenothiazines and, to a lesser extent, other antipsychotic drugs produce rather striking side reactions on the reproductive system. Amenorrhea, galactorrhea, false-positive pregnancy tests, and increased libido have been reported in women, while men have been troubled by decreased libido and gynecomastia. Six post-menopausal women treated for 60 days with thioridazine showed a significant decrease in total urinary gonadotropin excretion. Pituitary gonadotropin (FSH) was also found to be less than normal for adults in three of five women in whom amenorrhea and galactorrhea had developed (53). FSH excretion is probably diminished by chronic treatment with large doses, but reports are conflicting (54, 55). An increased production of luteinizing hormone (LH) has been suggested as a possible cause of false-positive immunological and biological pregnancy tests in phenothiazine-treated patients (56). As pointed out in a recent review of the endocrine actions of chlorpromazine, an explanation of how it produces amenorrhea and galactorrhea is not presently known (57).

Compared with a placebo group, patients treated with a combination of chlorpromazine and procyclidine in large doses (1200 and 15 mg daily, respectively) over a five-week period showed a significant rise in thyroidal uptake of radioactive iodine (27 to 36 per cent). Imipramine in doses up to 300 mg produced a smaller rise (27 to 29 per cent) (58). Trace amounts of iodine in some lots of perphenazine were finally held accountable for elevated serum protein-bound iodine values observed during a certain period of use of this drug (59). Clinically, little evidence of thyroid dysfunction has been observed (60).

Circulating adrenal steroids have decreased after treatment with chlor-

promazine in usual doses (61). A number of reports of decreased urinary excretion of adrenal steroids have also been published (62, 63). Some authors, however, have found no decrease either in 17-ketosteroids or 17-hydroxysteroids during periods on high oral doses of the drug (64). Still, an occasional patient on antipsychotic medication may be referred because of slight elevation in urinary steroids which return to normal when the drug is discontinued.

It has been hypothesized that chlorpromazine may cause temporary inhibition of "feed-back" tropins, such as FSH, LH and TSH, eventually overcome by the stimulus of a deficiency of the target hormones; while inhibition may be prolonged in the case of "unbalanced tropins," such as prolactin and somatotropin, where peripheral feed-back does not occur. This explanation might account for the galactorrhea and weight gain so frequently observed clinically. (65). However, it is difficult to explain satisfactorily the many endocrine side reactions.

Significant weight gain is commonly observed among patients taking phenothiazines. The gain in weight is independent of change in clinical condition, which makes it unlikely that it is a result in increased interest in food (66). Following discharge from the hospital, weight remained stable or decreased somewhat. Physical inactivity and a high-calorie diet were considered the most likely contributing causes for the weight gain during hospitalization (67).

Sporadic reports of cases of diabetes developing during chlorpromazine treatment continue to appear. Reversal of some of the biochemical abnormalities soon after discontinuation of the drug suggests a relationship. Glucose tolerance was decreased following single intravenous doses of 50 mg of chlorpromazine. *In vitro* studies suggest that the drug impairs the uptake of glucose by the rat diaphragm (68). Still, cases of diabetes definitely attributable to the drug or drug-induced obesity are rare.

Chlorpromazine, like other adrenergic blocking drugs, may temporarily lower serum cholesterol or serum triglyceride levels. A sharp decrease of serum cholesterol levels has been observed following relatively large doses (11 to 15 mg daily) of trifluperidol. Another butyrophenone also lowered serum cholesterol and caused an ichthyotic skin reaction (69). The latter is probably not related to the decrease in serum cholesterol levels, or to the apparent increase in serum demosterol levels.

Cardiovascular-respiratory effects:—Orthostatic hypotension and rapid resting pulse rates frequently result from use of the "high-dose" phenothiazines. Mean arterial pressure, peripheral resistance and stroke volume of chronic schizophrenics were decreased and pulse rate increased following daily doses of 1 to 3 gm of chlorpromazine (70). Elderly psychotic patients treated with acetophenazine or imipramine experienced a similar fall in blood pressure and increase in heart rate, but not when treated with the "low-dose" phenothiazine, trifluoperazine (71). Less hypotensive effect from the more potent phenothiazines was also indicated by a study using five volunteers to whom

5 mg intravenous doses of perphenazine or prochlorperazine were administered. No change in blood pressure response to tilt was observed 8 to 16 minutes after the injection. Sedation followed by restlessness appeared in one to three hours and lasted for one to two days (72).

Abnormal EKGs were observed in 17 of 22 chronic psychiatric patients treated with thioridazine, 4 of 23 treated with chlorpromazine, 2 of 21 treated with trifluoperazine, 1 of 3 treated with thiopropazate, and 3 of 11 treated with levomepromazine. Changes were a prolongation of the Q-T interval, and abnormal configurations of the ST segment and T-waves, the latter being rounded, flattened or notched (73). Abnormal T-waves from thioridazine appeared to be directly related to dose, with none present at daily doses less than 100 mg but present in 75 per cent of the patients receiving more than 300 mg. The lack of progression with time, the rapid reversion to normal after discontinuation of drug, and the pharmacological reversal by various drugs suggests a benign disturbance (74). Among drugs which are reported to reverse the abnormal T-waves are a nitrate (isorbide dinitrate), a potassium mixture, and an α-adrenergic blocking drug, ergotamine (75). Although animal studies often show disturbed cardiac conduction, such evidence has been conspicuously absent in patients with the usual T-wave abnormalities.

Cardiac arrhythmias have been observed from reserpine (premature ventricular contractions and short runs of ventricular tachycardia) and thioridazine (ventricular tachycardia). A number of sudden deaths of patients treated with phenothiazines strongly suggest a ventricular tachyarrhythmia, probably fibrillation, as the cause (76). Daily oral doses of 2 to 3 mg of reserpine did not affect the rhythm in seven patients with atrial fibrillation, but decreased the ventricular rate probably by depression of AV conduction (77). I have successfully reversed recently established atrial fibrillation by intramuscular administration of 5 mg doses of reserpine.

Most studies indicate little effect of chlorpromazine on respiration, either in healthy persons or in patients with underlying respiratory disease. The lack of effect of chlorpromazine alone was shown in normal volunteers, who received 25 mg intramuscular doses. However, when this dose was combined with 100 mg of meperidine, respiratory depression was more pronounced than from the same dose of meperidine alone (78). Thus, the use of these drugs for potentiation of analgesics may be at the cost of a synergistic depression of respiration.

The cardiovascular effects of the tricyclic antidepressants are similar to those of the phenothiazines; tachycardia and orthostatic hypotension are common. In usual therapeutic doses, both imipramine and amitriptyline may produce EKG changes similar to those produced by phenothiazines (79). Toxic doses of these drugs cause multiple cardiac arrhythmias. MAO inhibitors produce orthostatic hypotension used therapeutically on occasion.

Miscellaneous organs or systems.—A number of actions of these drugs have clinical importance as side reactions. Agranulocytosis has been the most

dire complication of treatment with phenothiazine derivatives, having been encountered with almost all of them, although rarely. The onset of this reaction early in the course of treatment, its independence of dose, and the rapid return of leukopenia on subsequent challenge with the drug have suggested an immunologic mechanism. Despite many attempts, leukocyte agglutinins have never been demonstrated in sensitive patients. Now it appears more likely that suppression of leukocytes is a direct toxic effect. Incorporation of H^3 thymidine into marrow cells is suppressed by chlorpromazine in many nonsensitive patients, although most adapt to this toxic effect when challenged with the drug. Patients who have shown marrow suppression incorporate thymidine slowly in any case, suggesting a limited proliferative potential to which the toxic effects of the drug may be added (80). Agranulocytosis has been observed from treatment with the tricyclic antidepressants. Clinically, the complication resembles that produced by the phenothiazines and, presumably, the mechanism is similar.

There is little evidence that phenothiazines have direct toxic effects on the liver. Cholestatic jaundice is apparently a manifestation of drug allergy (81). No doubt, many more such reactions are missed than are picked up, for liver biopsies early in the course of treatment reveal far more abnormalities than seen clinically. Yet, the clinical syndrome of cholestatic jaundice has been steadily waning for the past several years.

Recently, attention has been called to a pigmentary syndrome associated with chlorpromazine (82). The lens and cornea of the eye, the skin, and even possibly the viscera are involved. Histochemically, the pigment behaves like melanin, and is presumed to be melanin. Chlorpromazine and melanin form a charge-transfer complex, but the distribution of the pigment suggests that ultraviolet light is also essential to the localization (83). The melanin-chlorpromazine adduct may be of some relevance to the deposition of the drug in the body in highest concentrations in melanin-containing structures.

Interactions between drugs are enhanced by the polypharmacy widely practiced by psychiatrists. A number of instances of anticholinergic crises (bladder or bowel paralysis) have followed the concurrent use of anti-Parkinson drugs, tricyclic antidepressants, and phenothiazines. Recent evidence indicates that phenothiazines may lead to potentiation of anticholinergic effects of other drugs (84). Of far greater importance are the serious acute hypertensive reactions following the interactions of MAOI and a variety of pressor drugs and foods. The latter are those with high contents of tyramine, which is more common in foods than ordinarily believed. Thus, it is necessary to consider the pharmacology of foods. A number of excellent reviews of this subject have recently appeared (85, 86).

Drug Metabolism

Sulfoxidation, demethylation, N-oxide formation, and hydroxylation are the principal routes of metabolism of chlorpromazine (see Fig. 3). The demethylated and hydroxylated compounds are more active in animals than

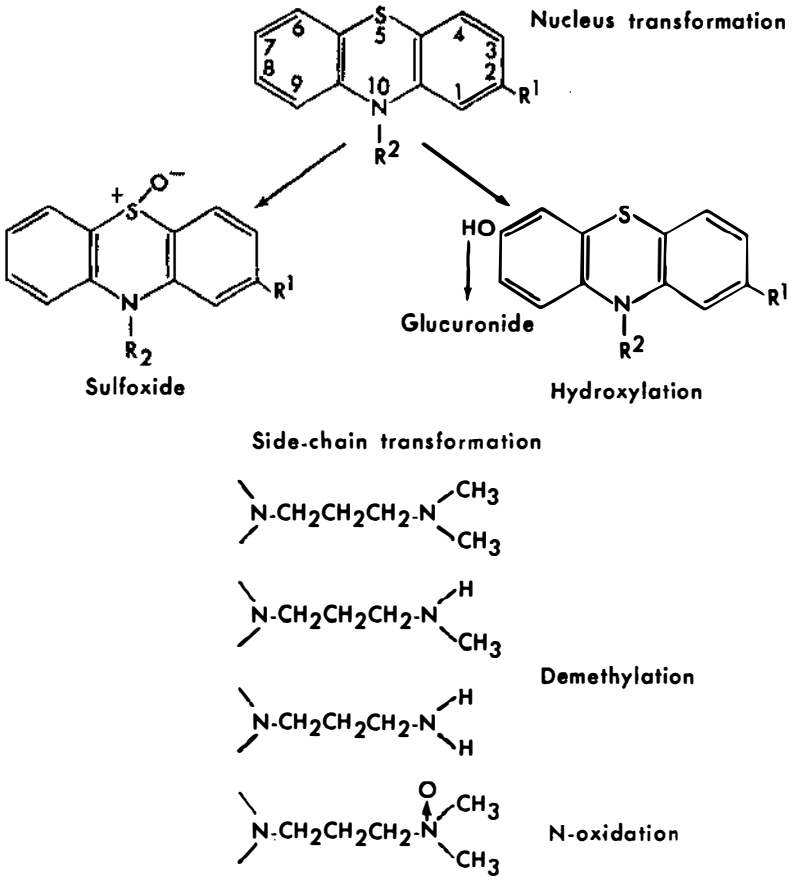


FIG. 3. Schema of chlorpromazine metabolism.

the sulfoxide which has a weak sedative action in man. The hydroxylated metabolites are conjugated with glucuronic acid and to a lesser extent with sulfate. Just on the basis of these metabolic pathways, over 150 metabolites are possible (89). In addition, some unusual but minor urinary metabolites have been described, such as 2-chlorphenothiazine and its sulfoxide (90). A chlorpromazine polymer with a hypothesized 1–2 linkage has been attributed to exposure to ultraviolet light and might be related to some photosensitivity reactions (91).

Phenothiazine metabolites found in human urine are outlined in Table I. Results have been quite variable, due to differing populations of patients, dosage regimens, and technical methods. Much of the metabolism of pheno-

TABLE I

URINARY RECOVERY OF PHENOTHIAZINE METABOLITES

DRUG	ACUTE DOSES	CHRONIC DOSAGE
CHLORPROMAZINE		
Total metabolites	7% (88)	58% (90)
		21–70% (95)
Glucuronides		45% (92)
N-desdimethyl monoglucuronide		predominant (88)
Hydroxylated compounds		5% (92)
Sulfoxide		8% (92)
Unchanged drug		1% (92)
Nor_1, nor_2-sulfoxide		7.7% (93)
N-oxide		less than sulfoxide (94)
THIORIDAZINE		
Total metabolites	30% (101)	1.4–18% (101)
		14–28% (102)
PROMAZINE		
Total metabolites		33% (104)
Norpromazine sulfoxide		6% (104)
Nor_1-promazine sulfoxide		5% (104)
3-hydroxypromazine glucuronide		4% (104)
3-hydroxy-nor_1-promazine glucuronide		3% (104)

thiazines and tricyclic antidepressants, both in animals and man, has been previously reviewed in this series (96).

The metabolic pattern varies considerably among patients, so it has been tempting to relate patterns of metabolite excretion to clinical response. However, evidence for such a relationship is still tenuous. The rate of relapse of 15 schizophrenics who were switched to placebo after chronic treatment with 600 mg daily doses, was not related to the duration of excretion of glucuronide metabolites, as the same investigators had previously thought (97). Still, the marked variation in relapse times and the prolonged excretion of metabolites following discontinuation of treatment suggests that many patients maintain effective tissue levels of drug for considerable periods following cessation of treatment.

Blood levels of drug have been difficult to measure and even more difficult to interpret. Plasma concentrations of chlorpromazine in patients chronically treated with 600 to 1200 mg daily doses usually range between 1 and 4 μg/ml, with small increases two to three hours after individual doses. Following an intramuscular dose of 100 mg, peak blood concentrations are attained in 30 minutes, and the drug has virtually disappeared from the blood after four hours (98). Blood concentrations apparently bear little relationship to clinical pharmacologic effects.

A complete post-mortem analysis of drug distribution was done on a patient, who received daily doses of 900 mg of chlorpromazine up to death. The concentration of drug in various parts of the brain varied from 1.6 to 9.5 μg/gm wet tissue, as compared with concentrations in hair of 124 μg/gm, lung, 97.5 μg/gm and liver, 13.5 μg/gm (99).

As thioridazine, like chlorpromazine, is usually given in fairly large doses, its metabolism in man has also been studied extensively. The possible metabolites of this drug are somewhat similar, although the piperidine side chain and the thiomethyl group at the 2-position of the phenothiazine ring permit a number of different types of metabolites. The pattern of excretion is shown in Table I.

Serum levels in 66 patients chronically treated with thioridazine ranged between 1 and 5 μg/ml, depending on the daily dose level; at doses of 600 mg, mean levels were about 3.5 μg/ml. Serum levels varied between patients, but were relatively stable in the same patient once an equilibrium was established after three to four days of treatment (103). Following single oral doses of ^{35}S ring-labeled thioridazine, only 3 per cent of the original dose was found in serum at peak levels three to four hours after ingestion (100).

Less is known of the metabolism of other antipsychotics. The pattern of excretion of promazine is outlined in Table I. Excretion of benzquinamide suggested a rapid and complete absorption of the drug following oral doses. Total urinary excretion of drug was 3 to 7 per cent following oral dises and 3 to 15 per cent following intramuscular doses (105).

Hydroxylation and N-demethylation are the principal metabolic pathways of the tricyclics. Hydroxylation may occur at either the 2- or 10-position; 10-hydroxylated compounds of imipramine, desmethylimipramine and didesmethylimipramine have been described. 10-Hydroxyiminodibenzyl may occur, as well as the corresponding glucuronides of these compounds (106). Imipramine N-oxide accounted for only 2 per cent of the dose of imipramine excreted in urine (107). Amitriptyline is metabolized in a similar fashion to imipramine.

Plasma levels of imipramine seven hours after a single dose of 100 mg averaged 6 μg/ml in four patients, who subsequently responded to treatment, and 13 μg/ml in four who were refractory. During subsequent treatment with daily doses of 150 mg, patients responding well to the drug had consistently lower levels than those who did not. Differential binding of the drug in the brains of various patients was suggested as an explanation for this paradox (108). Ring-labeled ^{14}C-amitriptyline was administered to one patient who showed plasma radioactivity in 30 minutes with a peak in about two to four hours. Over a 24-hour period, 35 per cent of the total radioactivity was recovered in the urine (109). Plasma levels of desipramine were followed in six women treated with 150 mg daily. Levels for individual patients remained relatively constant and the range of levels between patients (0.59 to 1.38 μg/ml) was not excessively wide. An inverse relationship be-

tween body weight and plasma concentration was suggested. Clinical response was not related to plasma levels of drug (110).

The monosubstituted hydrazine side-chain of phenelzine suggested that like hydralazine and isoniazid, it might be metabolized by acetylation. This process has been shown to be clearly polymorphic for isoniazid. Among 47 depressed patients treated with phenelzine, two groups of acetylators were found, slow and fast. Differences in clinical response to treatment were not apparent between the two groups, but the slow acetylators had many more side effects (111).

Biogenic amines.—When it was recognized that reserpine in animals impaired the storage capacity of the brain for 5-hydroxytryptamine (5-HT) for periods paralleling the duration of sedation, indirect studies were undertaken in man (112). Doses of reserpine, 4 mg daily, isocarboxazide, 30 mg daily, or a combination of these drugs, as well as a placebo were administered to 15 psychiatric patients. During periods of excited behavior, while the patients were on either drugs or placebo, marked increases in excretion of 5-hydroxyindoleacetic acid (5-HIAA) were noted. Conversely, during periods of tranquilization, excretion of 5-HIAA was decreased. It was hypothesized that the drugs may have a biphasic effect on 5-HT levels; large increases in brain concentrations of 5-HT correlating with excitement; moderate levels correlating with tranquility (113). A similar study, measuring tryptamine excretion, revealed that reserpine increased excretion only when the psychosis was aggravated. On the other hand, tryptamine excretion was regularly elevated following isocarboxazide, either alone or with reserpine, being related to the MAO inhibition rather than to behavioral changes. Neither drug had any effect on total catecholamine (epinephrine and norepinephrine) excretion unless some effect on sympathetic activity could also be observed (114). Reserpine given to schizophrenic men increased excretion of 5-HIAA and homovanillic acid (the end-product of DOPAmine metabolism), but decreased excretion of vanilmandelic acid (the end-product of catecholamine metabolism). Chlorpromazine produced similar effects which were not significant. No relationship could be discovered between the metabolic changes and therapeutic effects. The former were related to gastrointestinal and extrapyramidal side effects, however (115).

Single large doses of reserpine (10 mg) orally were associated with bodily discomfort and tranquilization for one to two days, miosis for seven days and decreased blood 5-HT for five weeks. Following a second dose five weeks later, miosis like 5-HT depletion was prolonged to five weeks, suggesting possible sensitization of brain amine mechanisms (116).

A relationship of catecholamine depletion to reserpine-induced sedation in man was suggested by the report that the psychological effects of the drug could be counteracted by administration of dihydroxyphenylalanine (DOPA), the precursor of catecholamines (117). The effects of this drug on catecholamine excretion in man have been variable. Intravenous doses of

70 μg/kg of reserpine or 0.5 mg/kg of guanethidine did not alter the urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA) over the next 24 hours (118). The time period may be crucial, for following single oral doses of 1 mg of reserpine, urinary excretion of homovanillic acid (HVA), the end product of DOPAmine metabolism, increased for a three-day period, after a lag of one day (119). A larger spectrum of catecholamines was measured following an intramuscular injection of 1.25 mg of reserpine in six retarded children; excretion of norepinephrine and its metabolite, normetanephrine, was decreased; excretion of epinephrine and metanephrine was increased; excretion of DOPA was decreased; and VMA excretion was increased. Similar changes followed chronic dosage. No consistent effect was noted on the rate of 5-HIAA excretion. Urinary DOPA was presumed to be decreased because more was being used in an effort to replenish the depleted stores of catecholamines (120).

Increasing evidence suggests a role for DOPAmine in the biochemical lesion of the Parkinson syndrome. Decreased DOPAmine excretion and a decreased concentration of this amine in basal ganglia have been reported in patients with this disease. A similar mechanism may be related to the extrapyramidal syndromes produced by drugs since single intramuscular doses of reserpine caused a marked increase in urinary homovanillic acid excretion, indicating DOPAmine release (121).

The recognition of reserpine-induced depression by clinicians and the later discovery of the effects of this drug in depleting the brains of animals of 5-HT and norepinephrine, led to the proposal that normally-occurring depressions might be associated with a deficiency of norepinephrine at central adrenergic synapses. Later, evidence indicated that two types of drugs used in treating depressions, the MAOI and the tricyclics, increase the levels of functional norepinephrine in the brains of animals. The norepinephrine hypothesis of depression has been proposed, therefore, to explain the biochemical pathogenesis of depression as well as the action of antidepressants. The evidence supporting this hypothesis and the problems in studying it further have been reviewed extensively elsewhere (122, 123). So far as studies in man are concerned, the measurement of levels of norepinephrine which derive almost entirely from tissues peripheral to brain is limited because of the blood brain barrier. Whether such studies are relevant to what is happening in the brain is still not certain. To some extent, the same difficulty applies to the study of all biogenic amines in their relation to the action of drugs on the brain.

Clinically effective doses of MAOI decrease excretion of VMA and 5-HIAA in man. A decreased excretion of these end-products of catecholamine and 5-HT metabolism is also found in depressed patients treated with imipramine or MAOI. Imipramine may decrease the neuronal re-uptake of norepinephrine as well as inhibit its spontaneous intraneuronal release and deamination. Both effects would be expected to increase normetanephrine excretion while reducing that of VMA (124). Intravenous in-

fusions of ^{3}H norepinephrine were given to 20 psychiatric patients before and after treatment with chlorpromazine, imipramine, and amitriptyline. The ratio of amine metabolites to deaminated metabolites was increased following treatment with all three drugs (125). MAO inhibition also increases the proportion of amine metabolites and markedly increases 5-HT and tryptamine excretion. Tryptamine may be of special importance because it freely crosses the blood-brain barrier. A hypothesis has been proposed for tryptamine-activated excitant receptors (126). Clinically, both tryptophan and 5-hydroxytryptophan have been reported to alleviate depressions in the presence of MAO inhibitors, but results are still equivocal. Similarly, DOPA, administered alone or in the presence of MAO inhibition, has had equivocally beneficial clinical effects. Peripheral effects of L-DOPA administered following ten days of pre-treatment with 100 mg daily doses of nialamide included elevations of blood pressure, flushing and palpitation in five normal subjects. Accumulation of DOPAmine, norepinephrine or both were postulated to produce these cardiovascular effects (127).

Clinical Considerations

The increasing number of chemicals with similar pharmacological actions and clinical antipsychotic activity has defied attempts at defining any meaningful structure-activity relationships. Some less important structure-activity relationships have been discovered clinically. At least two phenothiazines, mepazine and promazine, have been shown to be appreciably weaker antipsychotics than the rest (1, 128). In the case of promazine, the main difference is the absence of any ring-substituent at the 2-position. Apparently, substitution at this position makes the compound more lipid-soluble and increases potency. The most active phenothiazines in any of the three sub-groups (aliphatic, piperidine, and piperazine) are those with a tri-fluoromethyl substituent at this position. In the case of mepazine, ring substitution is also lacking; in addition, the piperidine side-chain is connected by a single carbon rather than by two carbons as in the case of thioridazine.

Side chains also characterize the compounds in other ways: the aliphatic series are more sedative with only moderate tendency to evoke extrapyramidal syndromes; the piperidine series, at least as exemplified by thioridazine, are quite sedative but lack extrapyramidal and antiemetic effects; the piperazine series are the most potent compounds, with less overt sedation and a high tendency to evoke extrapyramidal syndromes. Still, comparative studies of the antipsychotic effects of members of these sub-groups have shown no appreciable difference in therapeutic efficacy, provided equivalent doses are used (1–3). In most respects, the thioxanthene derivatives resemble the phenothiazines.

Despite the pharmacologists' infatuation with reserpine as a tool, it is not highly regarded as an antipsychotic by clinicians, since it is definitely less effective than phenothiazines (2). The drug is quite potent, as compared

with most phenothiazines, with a strong tendency to produce extrapyramidal reactions. Among these are uncontrollable restlessness, or akathisia. While this reaction may be seen with the piperazine phenothiazines, it is more of a nuisance with drugs such as reserpine, the benzoquinolizines, the butyrophenones, and molindone. The efficacy of these latter drugs, as compared with the commonly used phenothiazines remains to be elucidated, although it would appear that they may be equally effective (129, 130).

Attempts have been made to characterize patients who may respond selectively to one type of antipsychotic drug as opposed to another, especially in view of the clinical experience that patients who have been doing poorly may improve when switched to another drug. Despite a number of such attempts, any useful clinical categorization of patients is still lacking; at the moment, it appears that paranoid schizophrenic patients tend, as a general rule, to respond somewhat better than do nonparanoids, (130, 131).

The value of antidepressant drugs is far from being as clear as that of the antipsychotics; review of the major controlled studies on these agents indicates that the tricyclics are generally more effective than placebo, but not often as effective as electroconvulsive therapy (132). Results with the MAOI have been generally disappointing, with few studies showing any clear-cut superiority over placebo. The difficulty here may be that depressive syndromes respond differently to different drugs. Indeed, one may seriously question the concept of a special class of antidepressant drugs, as the two most commonly occurring types of depression have been shown to respond quite well to phenothiazines (133). The least common depressive syndrome, the retarded depression, responds almost selectively to tricyclic drugs (134). These clinical data may be highly relevant to the postulated biochemical pathogenesis of depressions and the proposed mechanisms of action of antidepressant drugs.

Toxicology

Poisoning with antipsychotic drugs is probably fairly common in clinical practice, yet it is rarely reported in the literature (135). Perhaps this is due to the almost uniformly favorable outcome. The few fatal cases of ingestion of chlorpromazine have all been in children, the minimal lethal dose being 350 mg. On the other hand, adults have survived doses of 9750 mg. No fatalities have been reported from excessive doses of chlorprothixine, reserpine, or haloperidol, following instances of large overdoses.

Progressive impairment of consciousness with an initial period of agitated delirium are the predominant clinical signs of poisoning from antipsychotic drugs. Twitching, dystonic movements, and convulsions are the principal neurological signs. EEGs may show diffuse slowing and low voltage. Tachycardia and marked hypotension are the principal cardiovascular manifestations. Hypothermia may be succeeded by hyperthermia; other vital functions may also be disturbed, leading to late respiratory failure, irreversible shock or cardiac arrest as causes of death.

Phenothiazines may be removed by gastric lavage, as most are readily water-soluble; however, once absorbed, firm binding to protein hampers attempts at removal by dialysis. Convulsions require treatment with anticonvulsants. Acute hypotension unresponsive to forced fluids may require use of a pressor agent such as L-norepinephrine. Other treatment is primarily supportive; maintenance of adequate airway, assisted ventilation, and environmental temperature controls.

The pharmacological resemblances of tricyclic antidepressants to phenothiazines are also evident in toxic doses which cause decreasing levels of consciousness, hypotension, body temperature disturbances, and convulsions. The major distinguishing feature of intoxication with these drugs is the occurrence of disturbances of cardiac rhythm and condition. These include ventricular flutter or runs of tachycardia, atrial fibrillation or tachycardia, and varying degrees of atrioventricular or intraventricular block. In addition, marked peripheral anticholinergic actions are evident. Anticholinesterases, especially pyridostigmine, have been effective in diminishing toxicity in animals treated with toxic doses of amitriptyline and may be worth trying clinically. Conversion of cardiac arrhythmias by electric shock is a technique to be considered in the face of persistent arrhythmias. Just as with phenothiazines, removal of these drugs prior to absorption is easy, but extremely difficult after they have been bound to protein.

Toxic doses of MAOI cause agitation, delirium, drowsiness progressing toward coma, tremors, seizures, and marked hyperthermia. Most of the toxic effects seem attributable to excessive adrenergic stimulation. Just as with amphetamine toxicity, chlorpromazine and other phenothiazines may be effective antagonists.

Conclusions

Despite the discovery of both antipsychotic and antidepressant drugs in the clinic and their application to disorders which are uniquely human, pharmacological studies of these drugs in man have not explained their modes of action. It seems clear that behavioral and other psychological effects of these drugs are quite poor predictors of their therapeutic potential or clinical responses. Although personality factors in the patient may have some importance in influencing the clinical actions, these appear to be, on the whole, less important than for most drugs which affect subjective experiences. The limitations of EEG studies in humans have been quite apparent, the paucity of substantial clinical EEG data contrasting greatly with the abundance of electrophysiological studies in animals. Investigation of drug metabolism, which may be the most advanced aspect of the human pharmacology of these drugs, has indicated that most have a cumulative action, that clinical effects are more dependent upon tissue levels than blood levels, and that patterns of metabolism still cannot be linked to differential clinical responses to drugs. The extent to which changes in biogenic amines can be measured clinically has limited confirmation of the important role of

these amines as well as the possible importance in their mechanism of action of changes in membrane permeability to them which have been suggested by animal experiments.

Investigation of the side effects of these drugs has been somewhat more rewarding. The unusual ability of many antipsychotic drugs to evoke extrapyramidal reactions in man has led to an extensive amount of investigation of the neurochemical basis of this disorder as well as possible new therapies. Depression, a side effect induced by reserpine, soon became a model for chemical studies which evolved into the norepinephrine hypothesis of depression, currently one of the most exciting aspects of the chemistry of emotional disorders.

As limited as the contributions of human pharmacology have been in this field, one can hope for development of hypotheses in the clinic which may be amenable to elaboration in the laboratory. These hypotheses in turn can be retested by further clinical experiments, at least within the restrictions which apply to any study of drugs in humans.

Glossary of Drug Names

ANTIPSYCHOTIC DRUGS

Phenothiazines: chlorpromazine (Thorazine); thioridazine (Mellaril); perphenazine (Trilafon); trifluoperazine (Stelazine); fluphenazine (Prolixin); prochlorperazine (Compazine); thiopropazate (Dartal); levomepromazine (Levoprome); promazine (Sparine).

Thioxanthenes: chlorprothixine (Taractan)

Rauwolfia alkaloids: reserpine (Serpasil)

Butyrophenones: haloperidol (Haldol)

Benzoquinolizines: benzquinamide (Quantril)

Phenylpiperazines: oxypertine (WIN 18501-2)

Indole derivative: molindone (EN-1733A)

ANTIDEPRESSANT DRUGS

Tricyclics: imipramine (Tofranil); desipramine (Pertofrane); amitriptyline (Elavil).

Hydrazide MAOI: Isocarboxazid (Marplan); nialamide (Niamid); iproniazid (Marsilid); phenelzine (Nardil).

Non-hydrazide MAOI: pargyline (Eutonyl); tranylcypromine (Parnate)

OTHERS: Promethazine (Phenergan); chlordiazepoxide (Librium); diazepam (Valium); meprobamate (Miltown); procyclidine (Kemadrin); meperidine (Demerol); guanethidine (Ismelin).

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