PSYCHOPHARMACOLOGY

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INTRODUCTION

Intense interest in psychopharmacology has generated many significant contributions to the literature on this subject. The selection of original research papers for this review has necessarily been restricted by space limitations, and also by the interests and biases of the authors. The large number of books appearing during the last year presents additional evidence for the continued growth of psychopharmacology. Some of these books have been listed in the bibliography (1–22) for the benefit of the interested reader.

This review is not concerned with clinical psychopharmacology directly but it may be appropriate to mention three publications which especially reveal the capacity of drugs to improve the symptoms of schizophrenia. In *Treatment of Schizophrenia* (21) a careful study revealed that the differences between psychotherapy plus drugs, and drugs alone, are often very small or trivial and never statistically significant. On the other hand, the clinical effectiveness of the anti-anxiety drugs is somewhat controversial because of a number of confounding variables which are nondrug in origin and which are discussed in *Non-Specific Factors in Drug Therapy* (22). According to Hollister (106) there appears to be a consensus that in the management of anxiety, meprobamate, chlordiazepoxide, diazepam, and oxazepam are slightly better than barbiturates and all are somewhat better than placebo. Moreover, various members of the imipramine group of drugs have shown superiority over placebo in the treatment of depressed patients. With further information on the biochemical aspects of psychotic or endogenous depression, we may expect more specifically directed therapy, and, therefore, improved clinical results.

PSYCHOPHARMACOLOGY IN MOOD DISORDERS

CURRENT CONCEPTS REGARDING THE BIOCHEMICAL BASIS OF MOOD DISORDERS

The concept of a relationship of the brain monoamines with disorders of mood had its origin in the important findings that drugs which excessively affect emotional tone in man also alter levels of one or more of the brain

amines in animals. By 1956, there was a drug that caused severe depression and reduced levels of the monoamines, i.e., reserpine, and a drug which elevated mood in depressed patients and increased levels of the monoamines, i.e., iproniazid. These findings were the springboard for a vast amount of psychopharmacological research which provided the background for several concepts regarding the roles of monoamines in pathological disorders of affect.

Since these drugs affected the metabolism of both serotonin and norepinephrine the question arose as to which of the two monoamines was more important in altering mood. The first expressions that a functional deficiency of the catecholamines might be involved in depression were those of Jacobsen (111) and Rosenblatt et al. (162). This view has become known as the "catecholamine hypothesis of affective disorders" and the supporting evidence has been reviewed (46, 169, 170). The hypothesis has been stated thus by Schildkraut (169):

> . . . some, if not all, depressions are associated with an absolute, or relative deficiency of catecholamines, particularly noradrenaline, at functionally important adrenergic receptor sites in the brain. Elation, conversely, may be associated with an excess of such amines.

Part of the supporting evidence for this hypothesis was obtained with an animal model of human depression, i.e., reserpine-induced behavioral depression. This model has been used in procedures for the depletion of amines followed by their selective replacement through the administration of the appropriate amino acid precursor. The amino acid precursor of the catecholamines, 3,4-dihydroxyphenylethylamine (DOPA) was found to reverse temporarily reserpine depression in animals (51) and in man (74). On the other hand, in studies in which DOPA has been administered to depressed patients (149, 150) little change in mood has been observed. However, not all DOPA studies have failed to show a reversal of depressive mood. Bunney et al. (47) have reported one case in which the response to DOPA was a dose-dependent phenomenon and they were able to demonstrate a sustained therapeutic response to the orally administered amino acid. Exacerbation of the depressive symptoms occurred when DOPA administration was stopped and a placebo substituted. They have suggested that there may be two classes of depression, with either a catecholamine deficit in which patients respond to DOPA, or a serotonin deficit in which patients respond to tryptophan.

There is recent evidence from animal studies that a reversal of reserpine-induced depression by DOPA may be a result of the formation of dopamine rather than norepinephrine. Havliček & Sklenovsky (102) have reported that the administration of 3,4-dihydroxyphenylserine (DOPS), an amino acid which can be decarboxylated to norepinephrine without dopamine being formed, resulted in deactivation of the electroencephalogram and behavioral depression. Creveling et al. (68) have demonstrated that behav-

ioral depression in reserpinized animals is reversed by DOPA administration but not by DOPS, although norepinephrine levels had been restored to normal by the latter amino acid.

A study in which an inhibitor of catecholamine synthesis, alpha-methyl-para-tyrosine, was administered to 20 patients, 11 of whom had pheochromocytomas, demonstrated sedation in 11 but the authors do not mention the occurrence of altered mood (184). Charalampous & Brown (54) also observed that this agent induced a marked sedative effect in a group of 17 mentally ill patients, most of them with schizophrenia. No anti-psychotic effect was found. An attempt to lower brain norepinephrine in manic patients with alpha-methyl-DOPA (139) did not alleviate the condition.

It has also been suggested that an altered metabolism of tryptophan is associated with affective disorders (57). An amino acid precursor of serotonin, 5-hydroxytryptophan (5-HTP), did not reverse reserpine effects in animals (51) or consistently benefit depressed patients when given in conjunction with a monoamine oxidase inhibitor (92, 119, 120, 149). However, it has been demonstrated that tryptophan when given with a monoamine oxidase inhibitor can elevate mood in mentally normal subjects (141), in depressed patients (60, 61, 92, 148), and in schizophrenic patients (127, 155). Tryptophan also has some mood-elevating activity when administered alone (61, 185). This amino acid has also been reported as beneficial when given prophylactically to one patient experiencing frequently recurring episodes of depression (103).

The potentiation of the antidepressant effects of monoamine oxidase inhibitors by tryptophan contrasts with the usual lack of effect of 5-HTP. A possible explanation for this difference may be found in the report of Moir & Eccleston (137) regarding the distribution of indoles in the brain after loads of tryptophan and 5-HTP. After tryptophan, but not after 5-HTP, the pattern of metabolism was similar to that of untreated animals. It has also been reported that the administration of para-chlorophenylalanine, an inhibitor of serotonin synthesis (121), to five patients with carcinoid tumors resulted in the appearance of psychiatric symptoms, mostly of an affective nature, in four (82).

In reviewing the biochemistry of the affective disorders, Coppen (57) has presented evidence that there are disturbances in three main areas: amine metabolism, electrolyte distribution, and adrenal cortical activity. There are disturbances of tryptophan metabolism in depression, as shown by decreased excretion of tryptamine (62), and decreased levels of 5-hydroxyindoles in cerebral spinal fluid (27).

The recent hypothesis of Lapin & Oxenkrug (126) posits that a deficiency of brain serotonin resulting from an altered metabolism of tryptophan occurs in depression. This view has been expressed thus:

> Psychic depression may result from deficiency of brain serotonin. It is suggested that in depression the production of tryptophane pyrrolase by the liver is stimu-

lated by raised blood corticosteroid levels. As a result, the metabolism is shunted away from serotonin production and toward kynurenine production.

A number of reports on adrenal function have suggested that blood levels of glucocortical steroids are elevated in depression (57, 84, 91, 163). However other recent papers have indicated that this correlation may not be as close as originally thought (44, 58, 164, 165). Mandell & Spooner (132) have reported the increased breakdown of C^{14}-tryptophan through the kynurenine pathway in one patient during a depressive phase and this shift in tryptophan metabolism was associated with a rise in the 17-hydroxycorticosteroids. Curzon & Green (72) have reported a decrease in brain serotonin in hydrocortisone treated animals.

The role of norepinephrine in the etiology of affective disorders is further obscured by the dichotomy of opinion regarding the behavioral effects of this amine. The catecholamine hypothesis is based on the view that norepinephrine is a behavioral excitant. Several lines of evidence have suggested such a role for norepinephrine. Systemic administration of norepinephrine sometimes results in an electroencephalographic alerting response, but Goldstein & Munoz (94) found that only 20 per cent of various animals tested developed an arousal pattern after this amine. Various behavioral stimulating agents, for example, amphetamine which releases norepinephrine in the periphery and also in the brain (52), and the administration of DOPA cause alerting. However, there is a growing body of evidence that norepinephrine or epinephrine administered in such a way as to cross the blood-brain barrier, i.e., intraventricularly, intracisternally, or to animals with an immature blood-brain barrier, produces behavioral depression. Much of this evidence has been tabulated by Mandell & Spooner (132) in a critique of current psychochemical research studies in man. Direct actions of norepinephrine or epinephrine on the central nervous system ranging from production of sedation and lethargy to unconsciousness have been reported in various mammalian species, e.g., cat, dog, man, sheep, rat, ox, and in young chickens. Dewhurst (75) has recently presented a new hypothesis regarding the action of norepinephrine and other amines in the central nervous system. Amines were classified into two main functional groups: type A amines, fat-soluble compounds with planar hydrocarbon structures (e.g., indolyl or phenyl) had an excitant action on behavior. Tryptamine and phenylethylamine were the most active amines in this group. The second functional group, type C, water-soluble amines (e.g., catechols) had depressant effects on behavior. Epinephrine and norepinephrine were active amines in this group. A third group of amines (type B) had biphasic actions, i.e., could excite and then depress. The activity of members of this group depended primarily on lipid solubility and not on whether the substance was an indoleamine, catecholamine, or phenylethylamine. Both dopamine and serotonin were classified with this intermediate group.

The Dewhurst hypothesis of cerebral amine function and the biochemical basis of mood and mood disorders is stated thus:

> Lowering of mood and some forms of depressive illness may be due to either a deficiency of excitant (type A) amines, or diminished responsiveness of the type A receptor. Psychosocial factors are co-determinants of complex behavioural responses. Elevation of mood and some manic states may be caused by an excess of excitant (type A) amines or increased A receptor sensitivity. Psychosocial factors are co-determinants of more complex behavioral features.

Action of Monoamines on Neurons of the Central Nervous System

The interpretation of the action of psychotropic compounds, and the delineation of the possible roles of monoamines in the etiology of mental disorders, would be advanced by definitive information concerning the effects of the monoamines, regarded as synaptic transmitters, on post-synaptic neurons. Pharmacological analysis of these amines and various drugs at the neuronal level of the central nervous system has been made possible by the technique of microelectrophoresis (70). This technique utilizes the property of ions to migrate in an electric field. Ionizable compounds can be injected into the immediate vicinity of single nerve cells and recordings made of the electrical events occurring in single neurons.

It has been found that norepinephrine has both inhibitory and excitatory action on the population of neurons responsive to this amine, and is without any effect on others. This dual action is considered a genuine phenomenon by Salmoiraghi (166) who suggests that two types of receptors could account for these observations. One possible explanation is that some responsive neurons have both types and others only a single type of receptor. A preponderance of neurons respond to microelectrophoretically applied norepinephrine with a depression of activity. In some cases, this inhibition has been associated with hyperpolarization of the neuronal membrane (80, 152). The predominantly inhibitory action of norepinephrine on responsive neurons has been demonstrated in many parts of the mammalian central nervous system: cerebral cortex (123, 124), pyriform cortex (128), caudate nucleus (39), olfactory bulb (38), thalamus (151), hypothalamus (40, 186), lateral geniculate body (71, 153), brain stem (28, 42), cerebellum (105), and the spinal cord (80, 81, 152). Norepinephrine is also predominantly inhibitory when applied to the Renshaw cells of the spinal cord (34, 81, 199).

Although serotonin has excitatory action on certain neurons of the medulla (28), it is predominantly depressant on responsive neurons in the cortex (158), lateral geniculate body (71), thalamus (26), hypothalamus (40), olfactory bulb (38), hippocampus (35), and spinal cord (152). Dopamine is inhibitory on the neurons of the caudate nucleus (39, 131) and cerebral cortex (124). In some neurons of the basal hypothalamus characterized as desmethasone sensitive (187), dopamine and norepinephrine have depressant actions with dopamine having a greater inhibitory effect than norepinephrine.

The intravenous administration of 5-HTP or L-DOPA has been demonstrated to alter the activity of single cells in the amygdaloid complex (78). After a few minutes latency, 5-HTP caused a reversible decrease in the discharge rate of amygdaloid neurons which correlated in the time of occurrence with 5-HTP effects upon amygdaloid "spindling" shown in a previous publication (79). Acceleration of nerve cell discharges was induced by L-DOPA in this structure.

Antidepressant Drugs of the Imipramine Class

Despite the therapeutic success of the tricyclic antidepressants in alleviating pathological depression, their mechanism of action is unknown. At the present state of our knowledge, the various effects of these drugs cannot be fitted into a framework that clearly delineates the site and mechanism of their therapeutic action.

Norepinephrine studies.—A currently held view is that the blockade of norepinephrine uptake by these drugs leads to an increased amount of the amine in the synaptic cleft, thereby potentiating the norepinephrine action and overcoming the functional adrenergic deficit posited by the catecholamine hypothesis of affective disorders. The potentiation of exogenous and endogenous catecholamines at peripheral adrenergic sites by the imipramine class of drugs, desipramine in particular, has been well documented (69, 118, 188). However, there is also evidence of adrenergic receptor blocking action by the tricyclic antidepressants (48, 110), which would tend to diminish norepinephrine effects. More recently, studies have been designed to explore the effects of the tricyclic antidepressant drugs on central adrenergic mechanisms. After administration of labelled norepinephrine intraventricularly (93) or intracisternally (168) to imipramine- or desipramine-pretreated rats, reduced levels of radioactive norepinephrine were found in the brain. These compounds concurrently increased the brain levels of normetanephrine-H^3 (168). Imipramine or desipramine given after the labelled amine had been injected intracisternally slowed the disappearance of radioactive norepinephrine and increased brain content of radioactive normetanephrine (168). These studies suggest that imipramine or desipramine may similarly inhibit re-uptake of released endogenous norepinephrine and thus increase amounts of amine available for receptor interaction. However, amitriptyline (171) was found to have no effect on uptake but there was an increase in the O-methylated metabolite of the amine as in the study cited above (168). With nortriptyline (66), the N-mono-methyl analogue of amitriptyline, no effects on either the uptake, metabolism or subcellular distribution of the intraventricularly administered radioactive norepinephrine could be demonstrated.

An interesting, although indirect argument supporting the catecholamine hypothesis has recently appeared (195) in connection with the actions of p-chloroamphetamine, a compound which reduces brain serotonin levels (154). When given to depressed patients this compound alleviates depression in some of them (195), although its effectiveness is much less than that of the

tricyclic antidepressants. These data were interpreted by van Praag et al. (195) as an argument supporting the catecholamine hypothesis. Presumably the antidepressant action is attributed to the altered balance between serotonin and norepinephrine, leaving a relative preponderance of norepinephrine in the brain.

The idea that the tricyclic antidepressants alleviate depression by potentiating norepinephrine effects is based on the assumption that this amine has an excitatory action on behavior. This view is in conflict with reports of the behavioral depressant action of intraventricularly or intracisternally administered norepinephrine (vide supra). Moreover, it has been reported (43, 133) that imipramine-like drugs antagonize rather than potentiate norepinephrine in the central nervous system. Brittain (43) found that pretreatment of mice with imipramine antagonized the depressant and hypothermic action of norepinephrine injected intracerebrally. A similar action of nortriptyline was noted by Cowell & Davey (66) but was attributed to a potentiation of the peripheral hyperthermic action of norepinephrine which escaped from ventricular spaces. In addition, Mandell et al. (133) have found that norepinephrine antagonized imipramine-induced hyperactivity in young chicks with immature blood-brain barriers. In a previous study, Mandell et al. (134) demonstrated that imipramine has a triphasic action on activity level: a short period of hyperactivity, a longer period of hypoactivity, and then a long period of hyperactivity. This third effect, and the decrease in normetanephrine observed in this study, were viewed as evidence consonent with the interpretation that imipramine acts to produce a post-synaptic blockade of the central adrenergic receptors. During the last phase of its action, imipramine antagonized the behavioral depressant effects of norepinephrine. These authors suggest that imipramine has many and complex effects on norepinephrine motility in the neuron, and the blockade of uptake, reported by some investigators, may occur during the second phase of imipramine action.

Other evidence, while still suggesting that a physiological substrate of depression is the central adrenergic system, indicates that the release of norepinephrine may be increased in some affective disorders. Rosenblatt et al. (161) have investigated differences in the metabolism of infused tritiated norepinephrine in three groups of subjects: six manic-depressed patients during their depressed phase, three normals, and three nonmanic depressed patients. There were no differences in the total amount of radioactivity excreted, but an increased ratio of nondeaminated amine to deaminated metabolite occurred in the manic-depressive, depressed group. That is, relatively more amine was excreted by these patients than patients in the other two groups. The authors interpret their findings as indicating an increased release of functional norepinephrine in the retarded depressive group. As the authors note, these findings apply only to peripheral events, since it is unlikely that much amine enters the central nervous system. They suggest that increased excretion of nondeaminated amines may represent a feed-back ef-

fect due to diminished responsitivity of the adrenergic receptor. This interpretation has some support in the observations of Prange et al. (156) that injected norepinephrine has much less effect on systolic blood pressure of depressed patients than on that of normal individuals.

Serotonin studies.—Although great emphasis has been placed on the interaction of norepinephrine and the tricyclic antidepressants, there is evidence that these drugs also alter serotonin metabolism. Gyermek (97, 98) has reviewed the literature of the antidepressant drug effects on serotonin and has suggested that this amine has an important role in the clinical effectiveness of these compounds.

Pharmacological studies of peripheral tissues have revealed considerable differences between the tertiary and secondary amines of the tricyclic antidepressant class of drugs. Numerous investigators (188 inter alios) have confirmed that the N-mono-methyl analogues, notably desipramine, are more potent than their parent compounds in affecting adrenergic mechanisms. This contrasts with the effects on serotonin responses where the highest degree of serotonin potentiation on the nictitating membrane was obtained with imipramine (97).

In *in vivo* studies of the relative effectiveness of various antidepressants in altering norepinephrine and serotonin accumulation by brain tissue, Carlsson et al. (49, 50) have found that imipramine has less effect than desipramine on central adrenergic neurons, but this order of effectiveness is reversed for the serotonergic neurons. Imipramine, and chlorimipramine even more so, effectively inhibited the accumulation of serotonin by central serotonergic neurons. *In vitro* studies (24, 36) of brain tissue have also demonstrated that imipramine has a greater effect than desipramine on serotonin accumulation. A comparative study (25) of several tricyclic antidepressants on the accumulation of C^{14}-serotonin by brain slices has shown that both imipramine and amitriptyline are considerably more potent than their respective N-mono-methyl analogues, desipramine and nortriptyline, in antagonizing this activity. In agreement with *in vivo* research (49), chlorimipramine was the most potent drug studied in antagonizing serotonin accumulation. Also in accord with these reports of a weaker action of the N-mono-methyl compounds is the finding of Palaic et al. (147) that desipramine was without effect on C^{14}-serotonin uptake in perfused brain of rats. A significant decrease in endogenous 5-hydroxyindoleacetic acid was found but no significant change in the amount of labelled metabolite was noted.

Components of depression.—Pathological depression is comprised of three major components in varying proportions (117, 129); (*a*) the sadness of mood associated with feelings of hopelessness and helplessness, and a tendency to suicide, (*b*) anxiety, and (*c*) inhibition. In assessing the current status of psychotherapeutic drugs, Hollister (106) has indicated that imipramine and amitriptyline are the drugs of choice for retarded, endogenous, or possible psychotic depressions characterized by blunted affect, lack of motor movements, and emotional withdrawal. The phenothiazines in com-

bination with imipramine or amitriptyline are useful for patients where anxiety is a predominant accompanying symptom, perhaps suggesting different biochemical parameters of depression are selectively altered by these drugs. According to Lapin and co-worker (125, 126), activation of central adrenergic mechanisms is responsible for psychoenergetic and motor stimulating effects of antidepressants but not for their mood-elevating action. It has also been suggested by Carlsson et al. (49) that blockade of serotonin re-uptake is involved in the mood-elevating action of the tricyclic antidepressants, whereas blockade of norepinephrine re-uptake promotes drive in the depressed patient.

It has been hypothesized (126) that a diminution of serotonin influence on the amygdala leads to activation on the amygdaloid complex, which results in anxiety, tension, increased formation of corticosteroids, and symptoms of psychic stress. The reversal of this trend by the imipramine class of drugs is thought due to their action in intensifying central serotonergic processes. The relatively greater effect of amitryptyline and imipramine on the disposition of serotonin by brain, and the greater clinical effectiveness of these drugs, as compared to their N-mono-methyl analogues, lends support to this concept of the action of the tricyclic drugs.

Lithium Studies

Clinical studies have demonstrated that lithium is effective in the treatment of mania. It may also benefit depression and have a prophylactic value against recurrent manic-depressive psychoses. Work in this important area has recently been reviewed by Schou (174). A review by this author (175) on the pharmacology and biochemistry of lithium ion is also available.

Biogenic amines.—There have been several biochemical studies of lithium effects on the biogenic amines. Pretreatment of rats with lithium (2.5 to 15 meq/kg intraperitoneally) did not alter norepinephrine content of brain but enhanced the depletion of this amine after synthesis was blocked by H44/68 (64). In this acute study, lithium did not affect the depletion of dopamine by H44/68 or that of serotonin produced by the tryptophan hydroxylase inhibitor H22/54. In a chronic study, which is more in accord with clinical use, Corrodi et al. (65) gave rats lithium carbonate in their food so that at the end of a three week period their plasma lithium levels were between 0.5 to 1.5 meq/l, the same concentrations as patients have with this treatment. In contrast to their previous findings, lithium did not influence norepinephrine at all after the inhibition of tyrosine hydroxylase. They suggest that the acceleration of norepinephrine turnover in their older work might be caused by stress produced by the intraperitoneal injection, and stress leads to an increased activity of rat brain noradrenergic neurons. Important too, they also point to the fact that the chronic effect of lithium to retard serotonin turnover is the same as the action seen with tricyclic antidepressants (63).

Slices of mammalian brain labelled with radioactive norepinephrine (31,

113) and serotonin (56, 113) release these amines when the slices are subjected to mild electrical stimulation of short duration. The release of H^3-serotonin (56, 113) and H^3-norepinephrine (113) was diminished by the presence of lithium, but not by other monovalent cations, in the perfusing medium. Brain slices from animals pretreated with lithium also showed a diminished release of amines.

Acute (168, 172) or chronic (172) administration of lithium chloride increased the disappearance of intracisternally administered H^3-norepinephrine from rat brain. No statistical differences in uptake into the brain tissue were noted, but the deaminated metabolites of norepinephrine represented a greater fraction of the total radioactivity after lithium treatment (172, 173).

Electrolytes.—The therapeutic efficacy of lithium salts in the treatment of mania, and the chemical similarity of lithium ion to sodium and potassium ions, has renewed interest in electrolyte metabolism in the affective disorders. The possibility exists that lithium may exert its clinical action through effects on the movement and distribution of sodium and potassium across the neuronal membrane. According to the ionic theory of neuronal excitability, the distribution of electrolytes across the neuronal membrane, with sodium mainly extracellular and potassium mainly intracellular, is the chemical basis for the resting potential of the neuron. Changes in the distribution of these ions across the cell membrane lead to changes in the resting potential and, therefore, changes in neuronal excitability.

Evidence obtained by isotope dilution techniques (59, 90) and whole body counts (30) suggests that sodium retention is greater than normal in depressed patients. Coppen & Shaw (59) found evidence of elevated residual sodium during depression, possibly reflecting an increase in intracellular sodium in this affective state. Shaw (176) has speculated upon a change in brain excitability in the affective disorders as a consequence of this apparent redistribution of sodium. An increase in intracellular sodium would reduce the resting potential and lower the threshold for excitation, suggesting a state of hyperexcitability. In this connection, Whybrow & Mendels (200) have recently proposed that an unstable state of central nervous hyperexcitability exists in depression and possibly in mania, and have presented evidence from several areas of research in support of this concept. Further information on electrolyte studies in the functional psychotic disorders, and the effects of lithium therapy on electrolytes, may be found in the recent review of Durell et al. (77). Electrophysiological studies in normal man (88) and in cats (33) have indicated that lithium pretreatment may decrease gross electrical activity of the brain.

Methysergide

Two drugs which exert salutary actions on mania, both seeming to diminish the effects of serotonin, though apparently not in the same way, are methysergide and lithium. The simultaneous reports by Dewhurst (76) and

Haškovec & Souček (101) that methysergide is of therapeutic value in mania has revived interest in the mechanism of action of this drug. But methysergide by the oral route has not proved to be effective (58a) in contrast with the intrathecal and intramuscular routes (100a). There is some evidence that methysergide inhibits the peripheral effects of serotonin, an action Baldratti et al. (32) ascribed to a blockade of serotonin receptor groups. But more important, methysergide can also inhibit the central actions of serotonin, for example, Oswald et al. (145) demonstrated that premedication with methysergide antagonized the accelerated onset of paradoxical sleep induced by tryptophan. Moreover, methysergide increased wakefulness and decreased both phases of sleep (190). In addition, the local application of methysergide into the area postrema eliminated the hypersynchronizing effect of intracarotid or intravertebral injections of serotonin (122).

The fact that methysergide may precipitate depression in some manic patients does not prove but, nevertheless, agrees with the concept of Coppen (57) that an impairment of serotonin mechanisms may be part of the pathogenesis of psychotic or endogenous depression in some patients and the possibility that methysergide blocks serotonin receptors. Is methysergide effective in mania because it blocks cerebral receptors responding to the essential effects of serotonin in the brain?

Electroshock and the Monoamines

In the treatment of depression, electroconvulsive shock is regarded as the most reliable modality of therapy and is credited with 80 to 85 per cent improvement (129). The tricyclic antidepressants, i.e., imipramine and amitriptyline, are considered only slightly less effective (60 to 70) per cent improvement), but the time lag from the beginning of pharmacotherapy to patient improvement, between one and two weeks, enhances the risk of suicide in some depressed patients. Infusion therapy of depressive states with chlorimipramine causes an onset of improvement as early as the second day.

The biochemical basis of the improved state of patients after electroconvulsive therapy has not been established. Several groups of investigators have recently demonstrated changes in the brain monoamines of animals subjected to variously administered electroshock. The most consistent finding is the increased turnover of norepinephrine (37, 116, 194). An increased turnover of dopamine has also been noted (37) but information on serotonin turnover is conflicting, with both increased (37, 193) after footshock and decreased (83) turnover having been reported after shock applied transcorneally.

The reports regarding brain levels of these amines also present some divergent results, but as noted by Bliss et al. (37) absolute levels are not true indicators of their dynamic state. Decreased levels of norepinephrine were found most frequently (37, 134, 136) although increased levels of this amine have also been reported (104, 116). Serotonin levels were frequently

increased (83, 104, 116, 193) although findings of no significant change (37, 136) or decreased levels (167) have been reported. The levels of dopamine were not affected in most acute experiments but after 30 daily shock periods, Ordy et al. (142) found reduced dopamine levels in the caudate nucleus of squirrel monkeys but no change in norepinephrine levels was noted. These diverse reports regarding levels probably reflect differences in the administration of shock, i.e., intensity, duration, site of application, the time interval after shock when amines were assayed, and whether brain parts or whole brain was used in the amine assay, as well as species differences. The increased turnover of norepinephrine may indicate increased discharge of amines due to increased neuronal activity. It appears that norepinephrine is utilized more rapidly than stores can be replenished in spite of increased synthesis (37) and a net loss of amine frequently occurs.

STUDIES OF HALLUCINOGENS IN MAN AND ANIMALS

Psychotomimetic drugs, especially mescaline, were used experimentally for many years in order to study the behavioral and other disorders they induced. With the discovery of LSD, and the small amounts required to induce behavioral disorders, as little as 1 μg/kg, the thought naturally arose that such substances might occur in the course of metabolism in human beings and be involved in their mental disorders. With the psychotomimetic agents, the subject may experience symptoms mimicking those of schizophrenia and characterized by the appearance of illusionary ideas, even of delusions and hallucinations, frequently visual in type. In addition, there are emotional and volitional disturbances. The subject, however, recognizes that his behavior is rendered abnormal, unlike a schizophrenic patient who may actually believe his false perceptions and thoughts.

We shall limit our remarks to three groups of these compounds. The first group consists of those related to the catecholamines, which again are divided into two subgroups: first, the phenylethylamine group, with mescaline as the prototype; and second, the substituted phenylisopropylamine group, of which amphetamine may be regarded as the parent substance. Shulgin et al. (182) systematically investigated psychotomimetic amphetamine derivatives to determine their structure-activity relationship as compared with the potency of mescaline. They found, for example, that in man 2,5-dimethoxy-4-methyl-amphetamine (DOM), commonly called STP, a substance which they synthesized, is approximately 80 times as potent as mescaline.

A second group consists of the indoleamines, of which LSD is a prime example and N-dimethyltryptamine (DMT) is another. DMT produced symptoms like those of mescaline and LSD (160, 189). A third group is formed of the cannabinols, including marijuana and its principle, tetrahydrocannabinol. Marijuana, usually taken in smoke, is only a mild euphoriant and sedative but in large doses it may provoke a toxic psychosis, and there

is no doubt that tetrahydrocannabinol is an effective psychotomimetic drug (108). The compounds forming these three groups of drugs exhibit widely varying potencies; for example, in man, N-dimethyltryptamine is four times more potent than mescaline, while LSD may be 3000 to 6000 times more potent. Despite these quantitative differences, the mental states which are produced by these three groups of psychotomimetic compounds are similar in the changes in behavior they evoke.

The indoleamine and catecholamine psychotomimetic groups seem to be interrelated in regard to their mechanism of action as suggested by Wolbach et al. (202), for not only do their members evoke the phenomenon of tolerance under repeated administration but they also show close cross-tolerance between the two groups. This cross-tolerance, however, does not apply to the cannabinols (109), which are not related chemically to the other series.

A possible neurophysiological basis for the common mechanism between the catecholamine- and the indoleamine-related psychotomimetics has been suggested by the studies of the Galesburg workers. This is not the place to review them, but rather to point to the latest investigation in that area, the results of which, in general, are characteristic of the former work. Using their technique of making sections of the brain just above and below the midbrain, as well as the first cervical level, Fujimori & Himwich (87) found that the nonpsychotomimetic d-amphetamine evoked EEG alerting at the midbrain area while DOM (STP) reacted at the medullary level. As has been shown previously by Bueno et al. (45) in the rabbit, part of the basis of the EEG reactions depends on a midbrain center for EEG alerting and the medullary center for the resting EEG. They, therefore, suggested that DOM (STP), as an example of a psychotomimetic drug, acts by inhibiting the medullary mechanism and removing its restraints on the midbrain locus. This difference in the chief sites of action between the psychotomimetic drug and its nonpsychotomimetic congeners in evoking EEG arousal is depicted in Figure 1.

Whether or not these observations on psychotomimetic drugs are related to compounds formed in the body is a provocative question. Pollin et al. (155) performed a series of experiments and showed that methionine and a MAO inhibitor (iproniazid) produced worsening in the behavior of schizophrenic patients. Their experiments fell in line with the earlier work of Osmond & Smythies (143), suggesting there was an abnormal transmethylation of a catecholamine compound in schizophrenia. This expectation seemed to be fulfilled when Friedhoff & Van Winkle (86) tentatively identified 3,4-dimethoxyphenylethylamine (DMPEA) in the urine of schizophrenic patients as the compound responsible for the pink spot obtained by chromatographic procedures.

But the significance of DMPEA and the pink spot are at present controversial. In animal experiments DMPEA successfully produced significant disturbances in behavior (196) while, in contrast, negative results were seen

AGENT	MECHANISM (EEG)	SITE	EFFECT	RESULT (EEG)
Non-psychomimetic	Alerting	Midbrain	Stimulate	Alert
Psychomimetic	Resting	Medulla	Inhibit	Alert

FIG. 1. Mechanisms and sites of EEG alerting induced by nonpsychotomimetic and psychotomimetic compounds. Nonpsychotomimetic congeners stimulate directly the midbrain center of EEG alerting and induce EEG arousal. In contrast, psychotomimetic congeners act by inhibiting the medullary center for resting EEG, releasing its restraint from the midbrain activating system, thus resulting in EEG alerting.

in psychotic patients (107) and in normals (181). But it must be remembered that the animals received relatively larger doses than human subjects. Furthermore, DMPEA is oxidatively deaminated in humans twice as rapidly as in mescaline (55). Unlike the negative psychotomimetic effects of DMPEA when given orally to human subjects, the intravenous injection of DMPEA was similar in action to small doses of mescaline and, in addition, its psychotomimetic actions were potentiated by pretreatment with nialamide (53).

In regard to the pink spot, Ridges et al. (157) showed a highly significant statistical association between its appearance and the diagnosis of schizophrenia, excluding paranoid schizophrenics. But there seems to be little doubt that the methods used for extraction by different investigators yield pink spots containing different kinds of substances. For example, Creveling & Daly (67) employed mass spectrometry, a specific method, and definitely proved the presence of DMPEA in the pink spot. In addition, they performed paper chromatographic analyses and suggested that in addition to DMPEA there may be six other components of the pink spot. On the other hand, Watt et al. (198) could not find DMPEA in the pink spot by the method they used. Moreover, though p-tyramine had been reported as a constituent of the pink spot by Boulton et al. (41), Watt and his co-workers (198) were not able to find that constituent in their pink spot. It is evident that a fresh approach must be applied before any agreement will be found.

The transmethylation hypothesis (115) has also been applied to the indoleamines in papers emanating from the Galesburg laboratory. In human subjects, among other dimethylated tryptamines such as bufotenine and 5-

methoxy-N-dimethyltryptamine, only N-dimethyltrytamine has been proved to be psychotomimetic (160, 189). The position of bufotenine in regard to humans is controversial, and behavioral disturbances evoked by 5-methoxy-N-dimethyltryptamine have been demonstrated in animals only thus far. But in schizophrenic patients with exacerbations of behavior provoked by the administration of either methionine or cysteine and a MAO inhibitor, it has been demonstrated by thin-layer chromatography that bufotenine, N-dimethyltryptamine, and 5-methoxy-N-dimethyltryptamine are excreted in the urine preceding a period of behavioral worsening and continuing through the period of exacerbation of symptoms after which the premedication behavior of the patients was restored (192). Narasimhachari (140), Himwich (103a) and their respective co-workers have been able to confirm the observations of Tanimukai and colleagues (192) in schizophrenic patients. But simultaneous observations on normal controls, studied under identical conditions, including administration of cysteine and a MAO inhibitor, revealed that the normals did not excrete these three substances nor did they exhibit behavioral disturbances. Brain enzymes capable of both O- and N-methylation of the catecholamines and related compounds, and O-methylation of indoleamines, have been described (29). Recently an enzyme in chick, rat, and human brain capable of the N-methylation of various indoleamines has been reported (138).

Among the psychopharmacologic studies in animals, an antagonistic action exerted centrally by LSD against serotonin has been demonstrated in an *in vitro* study by Kawai & Yamamoto (114). They reported that postsynaptic potentials evoked by optic tract stimulation in the superior colliculus of the guinea pig were depressed by the addition of serotonin to the medium in which the slices were bathed, but that in the presence of LSD, serotonin no longer caused a suppression of the potentials. Furthermore, they found that BOL, a nonpsychotomimetic LSD congener, which antagonizes serotonin in peripheral organs, failed to act against serotonin in this brain part.

Biochemically it has been demonstrated that LSD produces a small but significant increase in serotonin concentration (85, 89) accompanied by a decrease in its metabolite, 5-hydroxyindoleacetic acid (159, 183). Votava et al. (197) gave LSD to rats pretreated with reserpine. They, too, found that LSD elevated brain serotonin and decreased norepinephrine levels. In addition, the dopamine level was also diminished. Aghajanian et al. (23) studied in rats the influence of parenterally administered LSD on the activity of neuronal units in the caudal midbrain raphé area, which is rich in serotonin-containing neurons (73), and found that those units responded to LSD by a cessation of spontaneous firing. This depressant effect suggested to Aghajanian et al. (23) that LSD may decrease serotonin turnover by depressing the firing rates of neurons containing serotonin, and result in an increase of this amine. They further speculate that LSD might act "like" serotonin at a postsynaptic site and thus lead to an indirect inhibition of activity in serotonin-containing neurons.

PSYCHOPHARMACOLOGIC STUDIES OF THE SLEEP-WAKEFULNESS CYCLE

Studies of the effects of drugs on the sleep-wakefulness cycle have added a new facet to the field of psychopharmacology. It is generally accepted that in addition to wakefulness, there are two main phases of sleep. In one, the electrical activity of the cortex is characterized by spindles and slow, large-amplitude waves. This stage is therefore sometimes called slow-wave sleep. In the second phase of sleep, the cortical electrical activity is similar to that of the waking stage. Accordingly, this phase has been named fast-wave sleep, and it is also called activated sleep or paradoxical sleep. Because of accompanying rapid eye movements, it is frequently referred to as REM sleep. In man it is also named dream sleep for obvious reasons (146).

According to Jouvet (112), both phases of sleep are active processes and are modulated by the brain biogenic amines. Serotonin arising in the raphé nuclei plays a double role, first in the production of slow-wave sleep and second in "priming" activated sleep, while norepinephrine from the locus coeruleus "triggers" activated sleep, a process accomplished with the intervention of a cholinergic mechanism. For the investigations supporting this concept, the reader is referred to Jouvet's review (112).

Excellent reviews on the effects of psychoactive drugs on the sleep-wakefulness cycle have been presented by Hartmann (100) in man, and by Oswald (144) in animals as well as in man. A perusal of Hartmann's Table II shows that most psychotropic drugs, given in adequate doses, decrease activated sleep time in man. But the opposite effect may be observed with smaller doses, for example, Lewis & Evans (130) found in human subjects that a dose of 25 mg of chlorpromazine increased activated sleep but 100 mg reduced it. Hartmann's long list of dream sleep depressants includes among other drugs the barbiturates, the phenothiazines, meprobamate, the tricyclic antidepressants, the monoamine oxidase inhibitors, and the amphetamines. Caffeine and the benzodiazepines seem to be without effect on dream sleep, while in humans reserpine evoked an increase in percentage of dream sleep time. Williams et al. (201) found that reserpine produced a significant increase in REM sleep on nights following drug administration while L-tryptophan, a serotonin precursor, increased the amount of slow-wave sleep in all subjects and also the latency for the inception of REM sleep tendency in a few.

Contrary to results in man, reserpine depresses activated sleep in infrahuman mammals. At least in the cat (135), rat (95), and the rabbit (191), paradoxical sleep is suppressed, a result that might be expected from Jouvet's viewpoint on the roles of serotonin and norepinephrine in sleep. It is true that the smallest effective dose for suppressing paradoxical sleep in rabbits (191) is close to the range of the doses of reserpine which prolong paradoxical sleep in man. So we cannot be sure that the difference in action of reserpine in man and infrahuman mammals is a dosage effect for it may be due to a difference in species. LSD, like reserpine and unlike other psy-

chotropic drugs, seems to be species dependent. An increase in activated sleep by LSD was reported in man (96) and in the rat (99), while approximately the same dose of LSD decreased activated sleep in the cat (104a).

Growing animals.—Shimizu & Himwich (180) also noted that imipramine, chlorpromazine, propericiazine, haloperidol, amphetamine (179) and LSD (177) all diminished activated sleep time in growing kittens. In general, for all drugs studied, the effects were less marked in the younger subjects, the exceptions being for the higher doses of LSD and amphetamine. Moreover, the drug actions to curtail activated sleep were apparent earlier in neonatal life than those to decrease wakefulness. Two other exceptions should be mentioned: haloperidol was the only drug which did not diminish activated sleep time (178), and propericiazine was the only drug that did not decrease wakefulness (180).

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