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Biogenic Amines and Emotion

Pharmacological studies suggest a relationship between brain biogenic amines and affective state.

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The historic studies of Walter B. Cannon suggested that the biologically active amine "adrenaline" was secreted in response to stimuli which produced fear and rage reactions in animals (*1*); since then, the possible relationship of this and other biogenic amines to human emotions has generated considerable scientific interest. In the years following Cannon's work, the physiology and metabolism of the biogenic amines have been studied in various affective states, including normal and pathological anxiety, depression, elation, and anger. Research interest in this area was further stimulated during the past decade by the finding that many of the drugs used in the psychiatric treatment of patients with affective disorders (*2–4*) also caused significant changes in the metabolism and function of various biogenic amines, peripherally and centrally (*5, 6*).

Numerous recent reviews and symposia have covered many aspects of the extensive literature which may be pertinent to the relationship of biogenic amines to affect (*5–15*). The present review, which is more representative than comprehensive, concentrates primarily on studies in man, or on those studies in animals which appear relevant to interpretations of clinical phenomena. Several possible animal models of human affective states are also described, since these may prove to be of heuristic value, despite obvious differences between these behavioral analogs of emotion in animals and affective states in man.

Biology of the Biogenic Amines

The catecholamines, norepinephrine and dopamine, and the indole amine, serotonin, are the brain monoamines on which interest has focused. Norepinephrine is present in many areas of the brain, but the highest concentrations are found in the hypothalamus. Epinephrine, present peripherally in the adrenal medulla, occurs in the brain in very low concentration compared to the concentrations of norepinephrine. Highest concentrations of dopamine are found in the basal ganglia, and only lower concentrations of this amine are found in most other brain areas. Serotonin, while found in high concentration in various peripheral tissues, is also present in the brain in appreciable amount and is generally similar to norepinephrine in its distribution (*16, 17*). Regional distribution of biogenic amines in the brain has been extensively studied by the recently developed histochemical fluorescence method, and monoamine-containing neurons have been described (*18, 19*). High densities of such neurons have been found in the limbic system, which includes the hypothalamus and other functionally related brain structures which may be concerned with emotional state.

While norepinephrine functions as a chemical transmitter substance at the terminals of the peripheral sympathetic nervous system (*20*), the role of this and other amines in the central nervous system is far from clear. It is thought that, at synapses, which are the junctions of two adjacent neurons, the chemical transmitter released from the presynaptic nerve endings causes changes in the postsynaptic neuronal membrane potential, which may thereby generate a nerve impulse. It has been suggested that norepinephrine, dopamine, and serotonin may each function directly as a transmitter substance in the central nervous system. None of the biogenic amines has yet been definitively established as a chemical neuro-transmitter in the brain, however, and some investigators have suggested (*17, 19, 21–23*) that one or more of these amines may act instead as modulators or regulators of synaptic transmission mediated by some other chemical transmitter—for example, acetylcholine.

Norepinephrine is synthesized from the amino acid tyrosine, through the intermediates 3,4-dihydroxyphenylalanine (dopa) and dopamine; it is stored within the nerve in intraneuronal granules. These granules have been observed by electron microscopy to occur at presynaptic nerve endings, and their contents may be released into the synaptic cleft in response to nerve impulses. Norepinephrine discharged from neuronal endings in physiologically active form, by either nerve impulses or the action of sympathomimetic drugs, is inactivated mainly by cellular re-uptake or by enzymatic conversion by catechol-*O*-methyltransferase to form normetanephrine. Norepinephrine released intracellularly, either spontaneously or by reserpine-like drugs, may be inactivated mainly by mitochondrial monoamine oxidase, forming deaminated catechol metabolites—for example, 3,4-dihydroxymandelic acid—before leaving the cell; monamine oxidase may thus regulate tissue levels of norepinephrine (Figs. 1 and 2) (*10, 21, 24–26*). Secondary *O*-methylation or deamination reactions involved in the formation of 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, or VMA), the

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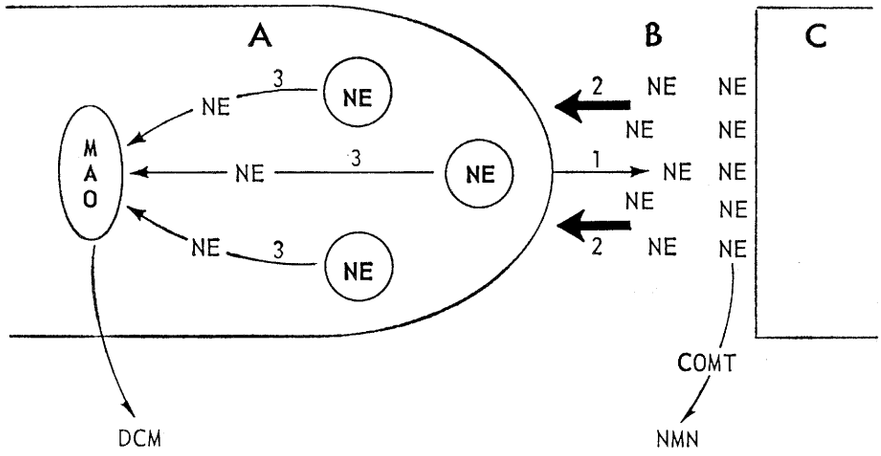

Fig. 1. Schematic representation of (*A*) a noradrenergic nerve ending, (*B*) synaptic cleft, and (*C*) receptor. *NE*, norepinephrine; *NMN*, normetanephrine; *DCM*, deaminated catechol metabolites; *COMT*, catechol *O*-methyltransferase; *MAO*, monoamine oxidase (within a mitochondrion); 1, discharge of norepinephrine into synaptic cleft and onto receptor; 2, reuptake of norepinephrine from synaptic cleft; 3, intracellular release of norepinephrine from storage granules into cytoplasm and onto mitochondrial monoamine oxidase.

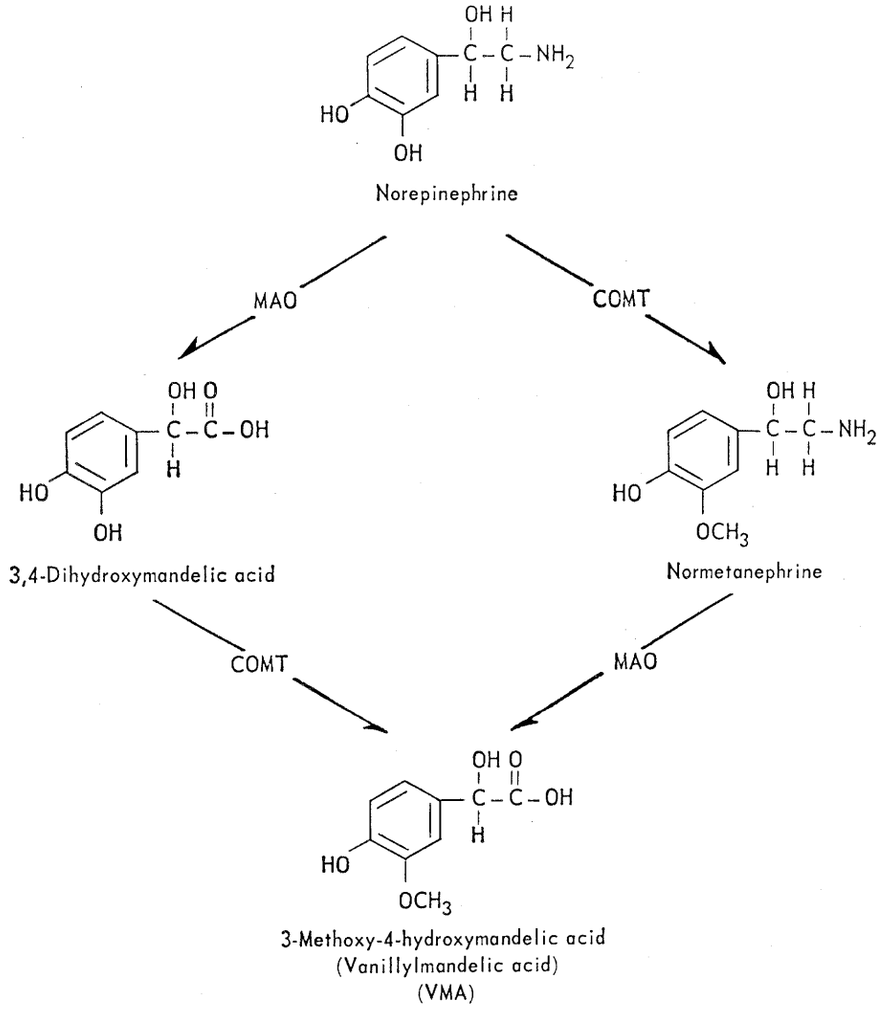

Fig. 2. Pathways of metabolism of norepinephrine (simplified). *COMT*, catechol *O*-methyltransferase; *MAO*, monoamine oxidase.

major urinary metabolite of norepinephrine and epinephrine in man, presumably can occur in the liver or kidney as well as in the nervous system (Fig. 2). While most of these concepts derive from studies of peripheral sympathetic nerves, similar patterns of metabolism appear to occur in the brain (*21, 27, 28*).

Epinephrine is synthesized from norepinephrine in the adrenal medulla by enzymatic methylation of the amine nitrogen. Activity of phenylethanolamine-*N*-methyltransferase, the enzyme involved in this reaction, has recently been shown to be enhanced by adrenocortical steroids (*29*).

Serotonin is synthesized from the precursor amino acid 5-hydroxytryptophan by decarboxylation and, like norepinephrine, may exist in the neuron in a bound and a free form. Serotonin is metabolized by monoamine oxidase, forming 5-hydroxyindoleacetic acid (*30, 31*).

Various aspects of the extensive literature on biogenic amine metabolism have been well reviewed recently, and the reader is referred to these summaries for more comprehensive coverage (*9, 24, 30, 32*).

Peripheral Catecholamines and Affective State

Some time after Cannon's work, norepinephrine was found to be secreted at sympathetic nerve endings (*20*) and was identified as a neurotransmitter at the terminals of the peripheral sympathetic nervous system. Epinephrine, however, was found to derive almost exclusively from adrenal medullary secretion in man (*33*). Norepinephrine appears not to cross the blood-brain barrier to an appreciable extent (*34, 35*); thus it is unlikely that the brain can be a significant source of circulating norepinephrine.

Attempts have been made by numerous investigators to relate secretion of norepinephrine or epinephrine to specific emotional states. From polygraphic measurements, Ax (*36*) concluded that the physiological response during anger resembled the reaction to an injection of norepinephrine alone, whereas the response during fear resembled the reaction to an injection of both norepinephrine and epinephrine. Funkenstein (*37*), in an extensive study of the cardiovascular responses of

psychiatric patients and normal subjects under psychological stress, found blood pressure changes associated with angry and aggressive states to be similar to those occurring during norepinephrine infusion, whereas the cardiovascular responses in states of anxiety or depression were similar to those observed during epinephrine infusion. In these studies, inferences concerning catecholamine secretion were made from data on physiological responses. In more recent investigations, catecholamines have been measured chemically. Mason *et al.* (*38*) have found, in the rhesus monkey, that increases in blood levels of epinephrine occurred in situations which combined uncertainty or unpredictability with the threat of noxious stimuli and anticipation of the need for coping behavior. Release of norepinephrine without concurrent elevation of the epinephrine level occurred when the conditions associated with administration of the noxious stimuli were familiar, unambiguous, and predictable.

Although momentary blood levels of the catecholamines may reflect with greater sensitivity their release in response to transient situations, the concentrations involved are low and the methods are fraught with difficulty, so that most investigators, when studying man, have relied upon urinary excretion for their measurements. Elmadjian *et al.* (*39*) found increases in norepinephrine excretion, with smaller increases in epinephrine excretion, in hockey players during active competition and in psychiatric patients showing aggressive emotional outbursts. Increases in epinephrine excretion alone were found in players who observed but did not participate in the game and in psychiatric patients during staff conferences. Euler and Lundberg (*40*) have observed increased excretion of both norepinephrine and epinephrine in aircraft pilots during moderately stressful flights; epinephrine excretion alone was increased in military personnel being transported by airplane as passengers. The effects of a variety of other stresses upon catecholamine excretion have been studied in Euler's laboratory, and these findings are summarized in a recent publication (*12*).

The psychological and physical effects of centrifugation on catecholamine excretion have been studied by Goodall (*41*). During the period of anticipation prior to centrifugation there was an increase in epinephrine but not in norepinephrine excretion, whereas, during centrifugation, the excretion of both amines was elevated. Silverman *et al.* (*42*) have found epinephrine excretion to be preferentially increased in anxious subjects, while norepinephrine excretion was relatively greater in angry or aggressive subjects who were studied under various experimental conditions.

During work performed under conditions of stress, improved performance was correlated with increased excretion of norepinephrine but not of epinephrine (*43*). In a study of catecholamine excretion in subjects viewing motion pictures selected to induce a variety of emotional states, Levi (*44*) found that bland, scenic films were associated with a reduction in urinary epinephrine and norepinephrine, whereas excretion of both amines was increased during emotionally evocative films (comedies or tragedies).

Although changes due to alterations in motor activity cannot be excluded in some studies (*12, 42*) and definitive interpretations of these findings may be limited by the relative lack of specificity of the catecholamine assay procedures, particularly in earlier investigations, these data seem generally compatible with the hypothesis that psychological and situational factors may differentially affect the relative excretion of epinephrine or norepinephrine. Increased epinephrine excretion seems to occur in states of anxiety or in threatening situations of uncertain or unpredictable nature in which active coping behavior may be required but has not been achieved. In contrast, norepinephrine excretion may occur in states of anger or aggression or in situations which are challenging but predictable and which allow active and appropriate behavioral responses to the challenge. Under various conditions, increase of either epinephrine or norepinephrine or of both of these catecholamines may represent specific adaptive responses; this appears to be an area where the conjunction of psychosocial, physiological, and biochemical investigation may be particularly rewarding (*8, 45*). The recent finding, in animals, that adrenocortical steroids enhance the activity of the enzyme which converts norepinephrine to epinephrine in the adrenal (*29*) may stimulate further study of possible functional interrelationships of these hormones in man.

The findings of changes in excretion of endogenous norepinephrine or epinephrine with various affective states are supplemented by data from studies of the psychological effects occurring with the exogenous administration of the catecholamines. Since the early studies of Wearn and Sturgis (*46*), investigators who have given human subjects infusions of epinephrine have reported the occurrence of subjective symptoms resembling anxiety (*47–50*). In many instances, however, these epinephrine-induced "anxiety states" have been clearly differentiated from true emotions by some experimental subjects, who reported feeling "as if" they were anxious, and these states were designated "cold" emotions by Maranon (*51*). Emotions other than anxiety after the administration of epinephrine have also been reported, and some subjects have experienced no emotional changes (*46, 48, 52, 53*). In contrast to the effects of epinephrine, less pronounced effects on emotion after the administration of norepinephrine have been reported (*49, 54, 55*).

It has been suggested that epinephrine infusion may produce a nonspecific state of arousal and that the past experiences of the individual subject and the characteristics of the experimental situation may be the factors which determine the quality and intensity of the elicited emotions. The limited data available from studies, relatively uncontrolled with respect to these variables, are compatible with this plausible hypothesis (*11, 47, 52, 54*). Schachter and Singer (*52*), in one of the few studies in which environmental cues have been controlled, have shown that, in experimental situations designed to produce either euphoria or anger, each mood was accentuated by administration of epinephrine but not by administration of a placebo. The relative passivity or activity of the subject, particularly with respect to the opportunity for effective expression of affect in the experimental situation, may also be of importance in determining whether anxiety or either anger or euphoria will be elicited (*52, 53*). More systematic and controlled studies of these intra-individual and situational factors will be required to test these hypotheses.

The blood-brain barrier effectively prevents the entry of epinephrine into the brain, except possibly in the region of the hypothalamus (*34*). Unresolved

is the question of whether epinephrine, administered or released peripherally, produces changes in affective state by a direct action on the hypothalamus or through subjective perception of its peripheral effects, which resemble those of anxiety. This controversy can be traced back to the original James-Lange theory of the visceral origin of emotions (*56*) and to Cannon's criticism of this formulation (*57*), which has been reviewed recently by Breggin (*11*).

Pharmacological Studies

During the past decade, a significant contribution to our understanding of the possible relationship of the biogenic amines to affective state has come from studies of the changes in metabolism of brain monoamines produced by clinically active psychotropic drugs. These studies have been the subject of several recent reviews (*6, 13, 45, 58*).

Reserpine and reserpine-like agents. Reserpine, which was used in psychiatry in the treatment of mania and excitement prior to the introduction of the phenothiazines and is used in general medicine in the treatment of hypertension, has been reported to produce severe depression of mood in some patients, particularly hypertensive patients treated with relatively large doses (*4, 59*). Discontinuing administration of the drug generally leads to remission of the depression. Depression has also been observed in patients given tetrabenazine, a drug which is similar to reserpine in its effects on biogenic amine metabolism (*60*). Such drug-induced depressions have been regarded by most observers as indistinguishable from naturally occurring depressive disorders, although this opinion has been questioned by some investigators (*61*).

The effects of reserpine have been extensively studied in experimental animals and in in-vitro systems (*62*). By a mechanism which has not yet been elucidated, reserpine interferes with the intraneuronal binding of the catecholamines and serotonin (*62*). With impairment of the binding mechanism by reserpine, these amines may diffuse freely through the cytoplasm and onto mitochondrial monoamine oxidase. This results in their inactivation by deamination and, thus, in depletion of tissue amine stores (*24, 25, 63*).

In animals, reserpine induces sedation, a state which has been proposed by some investigators as a possible animal analog of depression in man (*13*). This model has found practical application in the screening of potential antidepressant drugs. Reserpine-induced sedation in animals is associated with decreased brain levels of norepinephrine, dopamine, and serotonin (*58, 64*). Several congeners of reserpine have been prepared, and these show a good correlation between sedative action and the ability to reduce cerebral amines (*65*).

Since a fraction of the monoamines present in brain may be contained in reservoir pools, changes in the levels of the monoamines need not necessarily be associated with an alternation in function. Haggendal and Lindqvist (*66*), through long-term administration of reserpine in animals, depleted what are presumed to be the reservoir pools without producing chronic sedation. Having thus reduced the concentrations of monoamines in brain to about 10 percent of normal, these investigators then found an excellent temporal correlation, after each dose of reserpine, between the behavioral effects and the changes in the residual (possibly functional) pools of the three monoamines studied: norepinephrine, dopamine, and serotonin (*66*). Consistent with these findings have been the reports of a temporal association between the return of normal motor behavior in animals sedated with reserpine and the restoration of the brain's capacity to accumulate both norepinephrine injected into the cerebral ventricles and serotonin synthesized from the exogenously administered precursor 5-hydroxytryptophan (*67, 68*). These findings thus support the hypothesis that reserpine-induced sedation is related to impairment of the binding of monoamines; but the data do not allow separation of the effects of catecholamine depletion from those of serotonin release or depletion.

Further relevant data come from studies in which the amino acid precursors of catecholamines and serotonin have been administered to animals previously given reserpine. These precursor amino acids, unlike the monoamines, can cross the blood-brain barrier in animals and raise the concentrations of the respective monoamines in the brain (*69*). Administration of dihydroxyphenylalanine, the catecholamine precursor, reverses reserpine-induced sedation in animals and restores gross behavior and the conditioned avoidance response to approximately normal levels. The serotonin precursor, 5-hydroxytryptophan, however, does not restore normal functioning (*22, 69, 70*). Moreover, in one study involving human subjects, dihydroxyphenylalanine has been reported to counteract the psychological effects of reserpine (*71*). These findings suggest the importance of catecholamine depletion in reserpine-induced sedation in animals and, possibly, also in reserpine-induced depression in man.

The role of serotonin in the reserpine syndrome has been stressed by a number of investigators (*72, 73*). Some have suggested that serotonin produces central excitation and that depletion of serotonin contributes to the reserpine syndrome (*72*). Brodie *et al.* (*68*), however, have hypothesized that serotonin and norepinephrine exert antagonistic effects centrally and that free serotonin in the brain causes sedation. On the basis of kinetic considerations and other data they have concluded that the impairment of amine-binding by reserpine increases the free (unbound) serotonin available to occupy brain receptor sites and that this causes sedation in animals given reserpine; but this formulation has aroused some controversy (*21*).

The findings of recent studies with drugs which block the synthesis of serotonin or norepinephrine raise questions concerning the importance of serotonin in reserpine-induced sedation. The enzymatic hydroxylation of tryptophan is blocked by *p*-chlorophenylalanine, and brain levels of serotonin in animals have been reduced to less than 10 percent without changes in norepinephrine content. Sedation was not observed, under these conditions (*74, 75*). After administration of reserpine, however, animals whose brain levels of serotonin had previously been depleted through administration of *p*-chlorophenylalanine became sedated (*74*).

Catecholamine synthesis in the brain may be inhibited by α-methylparatyrosine, as discussed below, and norepinephrine levels may thereby be reduced without alteration in the serotonin levels (*76*). Spector *et al.* (*76*) observed sedation in animals when norepinephrine synthesis was interrupted by administration of α-methylparatyrosine. This finding has been confirmed (*68*), but not in all studies (*77*).

Some of the problems involved in establishing definitive evidence in this area have been discussed elsewhere (*45*). Much of the biochemical evidence has depended upon measurement of the

total brain content of one or another amine, or upon studies involving administration of precursor amino acids. The histological localization of the several endogenous pools of each of these amines (free and bound) has not been clarified, and there is now evidence, at least for norepinephrine in peripheral tissues, supporting the earlier speculation (*45*) that function may depend, not on the total content of an amine, but on the presence of a very small, but probably specifically localized, fraction (*21, 66, 78*), which may represent the newly synthesized amine. The distribution of amines formed from exogenously administered precursors, moreover, is not necessarily identical with the distribution of the endogenously formed amines (*79*). With these gaps in our basic knowledge, it is not surprising that, even after almost a decade of investigation, the problem of relating the phenomenon of reserpine-induced sedation to an effect of one or another specific amine, or their interaction, remains unresolved.

Monoamine oxidase inhibitors. Since the initial observation nearly 10 years ago of the antidepressant effects of iproniazid, a drug which inhibits the enzymatic activity of monoamine oxidase (*2*), numerous other monoamine oxidase inhibitors have also been reported to be effective in the treatment of depression (*80, 81*). Recent studies have indicated a correlation between clinical improvement in depressed patients and the degree of monoamine oxidase inhibition achieved during drug administration (*82*). Controlled studies of the clinical effectiveness of these compounds are limited, however, and there is some controversy concerning the relative clinical effectiveness of some of the monoamine oxidase inhibitors and the specific subgroups of depressed patients for whom these drugs are most indicated (*80, 81*).

In some animal species the monoamine oxidase inhibitors produce both behavioral excitation and elevated brain levels of norepinephrine and serotonin. This elevation of brain levels of monoamines presumably results from impairment by the enzyme inhibitor of normal metabolic inactivation by deamination. There has been some controversy over attempts to relate the behavioral excitation to increased concentrations of a specific amine (*5*). Spector and his co-workers, however, were able to separate these effects by using various inhibitors, doses, and animal species. They found that, in those species where the monoamine oxidase inhibitors elevated the levels of both norepinephrine and serotonin, the observed behavioral excitation was temporally correlated with the increase in levels of norepinephrine, whereas, in species in which there was an increase in serotonin without an increase in norepinephrine, no behavioral excitation was observed (*83*).

The monoamine oxidase inhibitors have also been found to counteract reserpine-induced sedation in animals (*58, 83–85*), and this behavioral change has also correlated better with changes in brain levels of norepinephrine than with changes in brain levels of serotonin (*21, 83*). Although definitive interpretation of such data on total brain content of amines is subject to the limitations discussed above, it seems plausible to hypothesize that the excitation which follows administration of monoamine oxidase inhibitors may be associated with the spillover of free norepinephrine onto receptor sites (*83*).

Reserpine-induced sedation is antagonized by prior treatment with monoamine oxidase inhibitors, and animals previously treated with a monoamine oxidase inhibitor show excitation and not the usual sedation after administration of reserpine (*84*). This has been ascribed to an accumulation of free active amines which are released by reserpine and cannot be inactivated by deamination.

Imipramine and the tricyclic antidepressants. Imipramine and other related tricyclic derivatives have been found to be the most clinically effective of the antidepressant drugs (*14, 81*). Although imipramine does not chemically inhibit either monamine oxidase or catechol *O*-methyltransferase, it has been found to potentiate both the response to sympathetic nerve stimulation in several experimental systems and many of the peripheral effects of exogenously administered norepinephrine in animals and in man (*14, 86, 87*). Potentiation, by imipramine, of the effects of serotonin in animals has also been reported (*86, 88*).

Hertting *et al.* (*89*) have found, in animals, that imipramine interferes with the uptake of infused norepinephrine into peripheral tissues, and have suggested that imipramine may decrease the cell-membrane or storage-granule-membrane permeability to this amine. Potentiation of the effects of norepinephrine by imipramine may thus result, in part, from impairment of the inactivation of free norepinephrine at the synapse by cellular re-uptake. This process would provide a mechanism for the "sensitization of central adrenergic synapses" which Sigg (*90*) had proposed to account for the antidepressant action of imipramine. Experimental evidence that imipramine inhibits norepinephrine uptake in the brain as it does in peripheral tissues has been reported recently by Glowinski and Axelrod (*91*). They, moreover, found that the chemically related tricyclic antidepressants desmethylimipramine and amitriptyline also inhibited norepinephrine uptake in the brain.

Following the intracisternal administration of H^3-norepinephrine into rat brain, Schanberg *et al.* (*92*) found that imipramine and desmethylimipramine increased brain concentrations of the *O*-methylated metabolite, H^3-normetanephrine, whereas chlorpromazine, a tranquilizer, did not. It has been suggested by a number of investigators that physiologically active norepinephrine which has interacted with receptors may be inactivated by *O*-methylation, but evidence supporting this plausible hypothesis is limited (*21, 93*). Eisenfeld *et al.* (*94*) have found, in peripheral tissues, that drugs which block adrenergic receptors decrease the formation of normetanephrine.

Prior treatment with imipramine can prevent reserpine-induced sedation in animals. This phenomenon has been shown, by Sulser *et al.* (*95*), to depend upon the availability and rate of release of catecholamines. When animals are first partially depleted of norepinephrine stores by administration of α-methylmetatyrosine, prior treatment with imipramine does not prevent reserpine-induced sedation. Scheckel and Boff (*96*) have found that small nondepressant doses of tetrabenazine caused excitation in animals previously treated with imipramine. This effect, too, can be prevented if catecholamine stores are first depleted by administration of α-methylmetatyrosine. These data seem compatible with the hypothesis that imipramine may exert its antidepressant action through potentiation of catecholamines at adrenergic receptor sites in the brain (*6, 7, 13, 90, 95, 96*).

Amphetamine. Amphetamine is a short-acting sympathomimetic psychic stimulant which has been used for many years with variable results in the treatment of depression (*97*). There is evidence that amphetamine may both re-

lease physiologically active norepinephrine from nerve cells and block the inactivation of norepinephrine by cellular re-uptake (*28, 98*). In studies of the metabolism of H^3-norepinephrine in the brain, Glowinski and Axelrod (*28*) have found that amphetamine increases concentrations of H^3-normetanephrine and decreases the content of deaminated tritiated catechols. Many of the behavioral effects of amphetamine are potentiated by imipramine (*96, 99*).

Large doses of amphetamine significantly lower the concentration of brain norepinephrine in animals (*100*), and amphetamine accentuates the decrease in brain norepinephrine induced by stress (*101*). Tachyphylaxis, a diminishing effect with repeated dosage, has been observed clinically, and the period of acute stimulation by amphetamine, particularly after large doses, is often followed by a "rebound period" of mental depression and fatigue (*97*). These observations may reflect a temporary depletion of norepinephrine stores available for continued release. While many observations suggest that amphetamine may release norepinephrine and potentiate the effects of this catecholamine at receptor sites, there is evidence that amphetamine may also exert a direct action at receptors (*102*).

Lithium salts. Lithium salts have been used in the treatment of elations (hypomania and mania) over a number of years, and their clinical effectiveness has been fairly well established (*103*). Schildkraut *et al.* (*104*; see also *92*) have recently found that lithium salts alter the metabolism of H^3-norepinephrine in the brain; concentrations of tritiated normetanephrine are decreased, while those of deaminated catechols are increased. It is unlikely that these changes are due to an inhibition of catechol *O*-methyltransferase, since lithium did not alter the activity of this enzyme in vitro (*92*). The changes in H^3-norepinephrine metabolites with administration of lithium are opposite to those observed with the euphoriant drug amphetamine (*28*). These findings are compatible with the hypothesis that lithium, a drug effective in the treatment of elations, may increase the intracellular deamination of norepinephrine and decrease the norepinephrine available at adrenergic receptor sites.

Alpha-methylparatyrosine. Spector *et al.* (*76*) have found that α-methylparatyrosine interrupts the synthesis of norepinephrine by inhibiting activity of the enzyme which converts tyrosine to dihydroxyphenylalanine. Sedation and impairment of motor activity have been reported to occur in animals when norepinephrine synthesis is interrupted through administration of α-methylparatyrosine (*76*; see also *68*) and Hanson (*105*) has reported disruption of conditioned avoidance behavior, which can be restored by treatment with dihydroxyphenylalanine; escape behavior was not impaired. Weissman *et al.* (*77, 106*) observed no sedation or disruption of conditioned avoidance behavior after animals were treated with α-methylparatyrosine, but found that the usual stimulation, by amphetamine, of gross behavior as well as of conditioned avoidance responding was blocked by α-methylparatyrosine and that the impairment of conditioned avoidance behavior by chlorpromazine was potentiated by α-methylparatyrosine. Differences in species or dosages may account for apparent discrepancies in these findings.

The pharmacological effects of this drug in man are currently under investigation. Preliminary study suggests that some patients receiving α-methylparatyrosine may experience transient sedation as dosage is increased and hypomanic-like reactions as the drug is withdrawn (*107*).

Possible models for the study of affective states. In the self-stimulation technique of Olds and Milner (*108*), an animal may, through implanted electrodes, deliver an electrical stimulation to its own brain by making some arbitrarily selected response such as pressing a lever. When electrodes are implanted in the lateral or posterior hypothalamus or certain other areas of the brain, animals will repetitively respond and induce brain stimulation without administration of external rewards. From these findings, a number of investigators have generated the hypothesis that a neuronal system for reward or pleasure may exist within the brain (*109*). Stein and others (*110, 111*) have suggested a possible relationship of this system to human affective experiences. While of heuristic value, this speculative formulation must be interpreted cautiously.

The technique of self-stimulation has been used to study the effects of psychoactive drugs. Stein has demonstrated (*111, 112*) an increase in the rate, and a lowering of the threshold, of self-stimulation in rats treated with amphetamine. These effects of amphetamine are potentiated by monoamine oxidase inhibitors or imipramine and counteracted by chlorpromazine. The effects of amphetamine are mimicked by phenylethylamine when inactivation of this substance is prevented by prior treatment with a monoamine oxidase inhibitor. After depletion of norepinephrine levels through treatment with reserpine or with α-methylparatyrosine, the inhibitor of tyrosine hydroxylase, the effects of amphetamine on self-stimulation are reduced (*111, 113*). Decrease in the rate of self-stimulation was observed after administration of tetrabenazine, a drug which releases, and depletes levels of, norepinephrine and other amines, but an increase in the rate occurred when tetrabenazine was administered to animals previously treated with a monoamine oxidase inhibitor (*114*).

These data seem compatible with the hypothesis that norepinephrine may function as a transmitter or modulator in the neuronal systems which are involved in the phenomenon of self-stimulation. Decreased norepinephrine content in the brain and decreased epinephrine levels in the adrenal following rage reactions induced by electrical stimulation of the amygdala in cats have also been reported. When electrical stimulation did not produce rage responses, catecholamine levels were unaffected (*115*).

These techniques of electrical stimulation of the brain may provide valuable approaches for the biochemical study of behavioral analogs of emotion in animals. Further investigation will be required, however, before these may be accepted as adequate models for human affective experience.

Clinical Studies in Patients with Affective Disorders

Catecholamine metabolism in patients with affective disorders (depressions and elations) has been studied by a number of investigators. Strom-Olsen and Weil-Malherbe (*116*) found urinary excretion of norepinephrine and epinephrine to be greater during the manic phase than during the depressed phase in patients with manic-depressive disorders. Shinfuku *et al.* (*117*) reported a similar increase in norephinephrine excretion during mania in a single patient with regular manic-depressive mood changes. Norepinephrine and epinephrine excretions were elevated in a large series of manic patients reported

by Bergsman (*118*). No significant change in the excretion of either amine was observed in the group of patients with endogenous depressions, but the patients with retarded depressions were not separately characterized (*118*). Increased urinary excretion of norepinephrine in depressed patients has also been reported (*119*).

In a longitudinal study of affective disorders, Schildkraut *et al.* (*120*) have observed a gradual rise in normetanephrine excretion during the period of definitive clinical improvement in depressed patients treated with imipramine. Normetanephrine excretion was found to be significantly lower, in patients with retarded depression, before treatment than after treatment with impramine when clinical improvement occurred. Increased normetanephrine excretion was observed in one patient studied during a hypomanic episode, which occurred without drug administration. The magnitude of the increase in normetanephrine excretion appeared to be related to the clinical severity of the hypomanic symptoms. In their studies of the effects of reserpine and sympathomimetic drugs on H^3-norepinephrine metabolism in animals, Kopin and Gordon (*25*) have adduced evidence compatible with the hypothesis that normetanephrine excretion may reflect noradrenergic activity. If this relationship also applies in man, the data on normetanephrine excretion in patients with affective disorders would suggest that increasing noradrenergic activity may be associated with the period of definitive clinical improvement from depression, and that noradrenergic activity may be relatively decreased in retarded depressions and increased in mania (*120*).

Caution must be exercised, however, in interpreting such data on the urinary excretion of norepinephrine and metabolites, since factors other than affective state—for example, muscular activity —may produce significant changes (*121*). Moreover, a blood-brain barrier to normetanephrine similar to that known to exist for norepinephrine has recently been described in animals (*27*). It is, therefore, probable that only a small fraction of urinary norepinephrine or normetanephrine derives from the brain. Nonetheless, such data on the urinary excretion of norepinephrine and metabolities are of interest, since biochemical changes in catecholamine metabolism in the periphery may reflect similar changes occurring centrally, and an increase in peripheral sympathetic activity may reflect increased central noradrenergic activity.

In studies of the urinary metabolites of infused radioactive norepinephrine in psychiatric patients, Rosenblatt and Chanley have reported (*122*) an elevated ratio of amines to deaminated acid metabolities in a subgroup of patients with retarded depression whom they classified as manic-depressive. The definitive interpretation of this finding, however, is not immediately apparent in the light of the studies on endogenous norepinephrine and metabolities.

A number of studies (*7, 123*) have shown that clinically effective doses of the monoamine oxidase inhibitors decrease excretion of 3-methoxy-4-hydroxymandelic acid (VMA) and 5-hydroxyindoleacetic acid in man. Decreased excretion of 3-methoxy-4-hydroxymandelic acid has, moreover, been found in depressed patients during treatment with imipramine or with monoamine oxidase inhibitors (*7, 124*). It has been suggested that imipramine, which inhibits cellular re-uptake of norepinephrine, possibly by decreasing membrane permeability to norepinephrine, might also inhibit the spontaneous intracellular release and deamination of norepinephrine. Inhibition of norepinephrine synthesis may also occur. Decrease in excretion of 3-methoxy-4-hydroxymandelic acid during short-term and long-term treatment with chlorpromazine has also been reported (*125*).

Alterations in the metabolism of the indole amines have been reported in patients with affective disorders. Ashcroft and Sharman observed a decrease in the concentration of 5-hydroxyindoles in the cerebrospinal fluid of depressed patients (*126*). A decreased rate of liberation of $C^{14}O_2$ from administered carboxy-labeled 5-hydroxy tryptophan was found by Coppen *et al.* (*127*). These investigators have recently reported urinary tryptamine excretion to be relatively decreased in depressed patients prior to treatment, and increased to approximately normal levels following clinical improvement. Most urinary tryptamine is probably not of central origin but may derive from the decarboxylation of tryptophan in the kidney (*128*).

The amino acid precursors of serotonin and norepinephrine will cross the blood-brain barrier; these have been administered to human subjects and their effects on mood studied. Of the several amino acids administered in conjunction with a monoamine oxidase inhibitor, tryptophan was the only one found to produce mood elevation in chronic schizophrenic patients (*129*). On that basis, tryptophan was tested by other investigators and found to potentiate the therapeutic effects of monoamine oxidase inhibitors in depressed patients (*130*). Tryptophan administered alone to normal subjects has been found to produce various clinical signs and symptoms, including euphoria and drowsiness (*131*). The antidepressant activity of monoamine oxidase inhibitors has also been reported (*132*) to be potentiated by 5-hydroxytryptophan, but this effect could not then be replicated in a subsequent study, and other investigators have not observed this effect with 5-hydroxytryptophan (*133*).

Dihydroxyphenylalanine, the precursor of norepinephrine, administered alone or with a monoamine oxidase inhibitor, was not found to be effective in the treatment of depression by either Pare and Sandler (*133*) or Klerman *et al.* (*134*). More recently, Turner and Merlis (*135*) have reported mood elevation in a group of patients treated with a monoamine oxidase inhibitor and dihydroxyphenylalanine, and Matussek (*136*) has observed transient improvement in depressed patients following short-term administration of dihydroxyphenylalanine. The possible therapeutic effectiveness of dihydroxyphenylalanine and monoamine oxidase inhibitors in the treatment of depression, therefore, merits further careful study. It must be noted, however, that this combination of drugs may produce severe hypertension and cardiac arrhythmias (*137*).

Corresponding to the finding that reserpine-like agents produce excitement in animals previously treated with imipramine, clinical improvement has been observed when reserpine or tetrabenazine has been added to the therapeutic regimen of a small number of depressed patients who had failed to respond to tricyclic antidepressants alone (*138*). Further study, however, will be required to document this important finding.

Electroconvulsive therapy, well established as an effective treatment for some depressed patients, has been studied by several investigators in an effort to determine whether the clinical effects were associated with an alteration in amine metabolism (*139*). Increases in plasma and urinary concentrations of norepinephrine and epi-

Table 1. Summary of the pharmacological observations compatible with the catecholamine hypothesis of affective disorders.

Drug	Effects on mood in man	Effects on behavior in animals	Effects on catecholamines in brain (animals)
Reserpine	Sedation Depression (in some patients)	Sedation	Depletion (intracellular deamination and inactivation)
Tetrabenazine	Sedation Depression (in some patients)	Sedation	Depletion (intracellular deamination and inactivation)
Amphetamine	Stimulant	Stimulation Excitement	Releases norepinephrine (? onto receptors) Inhibits cellular uptake (and inactivation) of norepinephrine
Monoamine oxidase inhibitors	Antidepressant	Excitement Prevents and reverses reserpine-induced sedation	Increases levels
Imipramine	Antidepressant	Prevents reserpine-induced sedation Potentiation of amphetamine effects	Inhibits cellular uptake (and inactivation) of norepinephrine ? Potentiates action of norepinephrine (as in periphery)
Lithium salts	Treatment of mania		? Increases intracellular deamination of norepinephrine ? Decreases norepinephrine available at receptors
α-Methylparatyrosine	Sedation (transient) with hypomania upon withdrawal	Sedation (in some studies)	Inhibits synthesis

nephrine after unmodified electroconvulsive therapy have been reported, but these changes are markedly diminished when barbiturates or muscle relaxants are used. It has been suggested (*140*) that, in animals, increased permeability of the blood–cerebrospinal-fluid barrier to norepinephrine occurs after electroconvulsive therapy.

Conclusion

The studies discussed here have shown a fairly consistent relationship between the effects of drugs on biogenic amines, particularly norepinephrine, and affective or behavioral states. Those drugs which cause depletion and inactivation of norepinephrine centrally produce sedation or depression, while drugs which increase or potentiate brain norepinephrine are associated with behavioral stimulation or excitement and generally have an antidepressant effect in man (Table 1). From these findings, a number of investigators have formulated the concept, designated the catecholamine hypothesis of affective disorders (*6*), that some, if not all, depressions may be associated with a relative deficiency of norepinephrine at functionally important adrenergic receptor sites in the brain, whereas elations may be associated with an excess of such amines.

It is not possible either to confirm or to reject this hypothesis on the basis of currently available clinical data. Although there does appear to be a fairly consistent relationship between the effects of pharmacological agents on norepinephrine metabolism and on affective state, a rigorous extrapolation from pharmacological studies to pathophysiology cannot be made. Confirmation of this hypothesis must ultimately depend upon direct demonstration of the biochemical abnormality in the naturally occurring illness.

It should be emphasized, however, that the demonstration of such a biochemical abnormality would not necessarily imply a genetic or constitutional, rather than an environmental or psychological, etiology of depression. Whereas specific genetic factors may be of importance in the etiology of some, and possibly all, depressions, it is equally conceivable that early experiences of the infant or child may cause enduring biochemical changes and that these may predispose some individuals to depressions in adulthood.

It is not likely that changes in the metabolism of the biogenic amines alone will account for the complex phenomena of normal or pathological affect. Whereas the effects of these amines at particular sites in the brain may be of crucial importance in the regulation of affect, any comprehensive formulation of the physiology of affective state will have to include many other concomitant biochemical, physiological, and psychological factors. Although in this review of the relationship of biogenic amines to affective state relatively little has been said concerning the intricate set of environmental and psychological determinants of emotion, the importance of these factors must be stressed.

The normally occurring alterations in affective state induced by environmental events is well known to all, from personal experience. The interactions between such environmental determinants of affect, various physiological factors, and the complexity of psychological determinants, including cognitive factors derived from the individual's remote and immediate past experiences, have received only limited study under adequately controlled conditions. It may be anticipated, however, that this will prove to be a particularly fruitful area for future research, for only within such a multifactorial framework may one expect to understand fully the relationship of the biogenic amines to emotional state.

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The Kirchhoff-Planck Radiation Law

Considering Kirchhoff's law as it was initially meant may help us understand the rise of quantum theory.

Joseph Agassi

It is well known that Planck studied Kirchhoff's radiation law because he was attracted by its utter generality, and that he was thus led to his theory of the quantization of light. Why this stress on utter generality? Did Wien, for instance, in studying Kirchhoff's law, disregard its generality? Are not all laws of nature general, and attractive on account of their generality (*1*)?

Moreover, how general, precisely, is Kirchhoff's law? One may say it applies to all *thermal* radiation of all *black* bodies which are in *equilibrium* with their environments. The previous sentence contains three restrictions: the radiation has to be thermal, the radiating body black, and the setup that of thermal equilibrium. We may omit any one of these restrictions and obtain three different interpretations of the law; we may omit any two of these restrictions and obtain three more interpretations; and we may omit them all. Thus we can have at least eight (empirically) different interpretations of the law. I say at least eight different interpretations because we may also interpret terms like *thermal radiation* differently. The most radically narrow interpretation of this term will be (intentionally) circular: that radiation is thermal which obeys Kirchhoff's law. This interpretation is so narrow that, once we restrict the law to thermal radiation in this interpretation of the word, we obviously do not have to restrict the law any further; it becomes an immediate corollary to the definition and thus trivially a tautology. This is, indeed, how *Handbuch der Physik* introduces the law (*2*, p. 133). There is, however, an elaborate proof of the law (*3*), in which the second law of thermodynamics is used, and so, evidently those who accept the proof accept a different interpretation of the law. One might expect—quite a priori, indeed—to be able to read from the proof the right interpretation. In fact, however, all eight interpretations mentioned above are found in the introductory literature, even in the leading introductory literature (*4*), not to mention works which are ambiguous about this point, or even inconsistent. I do not speak of marginal works; I need not discuss the importance generally and

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