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Catecholamine hypothesis of affective disorders

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CATECHOLAMINE HYPOTHESIS OF AFFECTIVE DISORDERS

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INTRODUCTION

Nosology and Etiology

Many discrete entities have been grouped together as the schizophrenic or affective disorders. An anology for this formulation has been recent findings on mentally deficient patients in which the mental deficiency can be caused by a number of separate discrete entities, each of which is characterized by a distinct, genetically controlled, biochemical abnormality. It must be recognized that the problem of schizophrenia and affective disorders may not be solved so simply and that multifactor or field theories of etiology may be more compatible with the clinical and experimental data. Such theories imply simultaneous occurance of experiential, and constitutional biochemical factors in order to give rise to a given clinical state.

Genetics

The genetic studies of twins suggests a hereditary basis for a number of psychiatric disorders and gives support to biological factors in mental illness. The "inborn error of metabolism" and "one gene one enzyme" hypotheses of Garrod and Beadle upon which contemporary biochemical thinking is based, has achieved substantial

support through the discovery of discrete enzymatic lesions underlying many inherited diseases including mental deficiencies. However, the permanency of a detectable enzyme defect cannot be assumed because it is possible that certain genetically controlled enzyme defects may be transient and occur only in response to specific environmental conditions or critical stages in development. These may still give rise to permanent structural changes in the nervous system and in learning experience, consequently giving rise to behavioral change without detectable enzyme abnormality. Other proponents of an organic etiology of schizophrenia and affective disorders have suggested acquired abnormalities such as autoimmune reactions or viral infections, but these are not generally accepted by contemporary investigators.[1]

The Catecholamine Hypothesis

Biochemical studies of affective disorders comprise an extensive literature which until recently has contributed little to the understanding of the biochemical mechanisms which may underly these disorders. Recently, the introduction of a number of drugs capable of producing both profound mood changes in human subjects, and alterations of brain amines in animals, has focused interest on the possibility that a disorder in brain metabolism may underlie affective illness. I therefore will present in this thesis recent selected studies involving drugs affecting amine metabolism

which support the catecholamine hypothesis of affective disorders. This hypothesis is based on the proposal that depressions are related to an absolute or relative depletion of catecholamines at functionally important sites in the brain and that elations may be associated with an excess. Other areas of research that will be mentioned include the use of lithium carbonate in manic depressive psychosis, and carbohydrate metabolism in depression.[2]

Review of Monoamine Metabolism

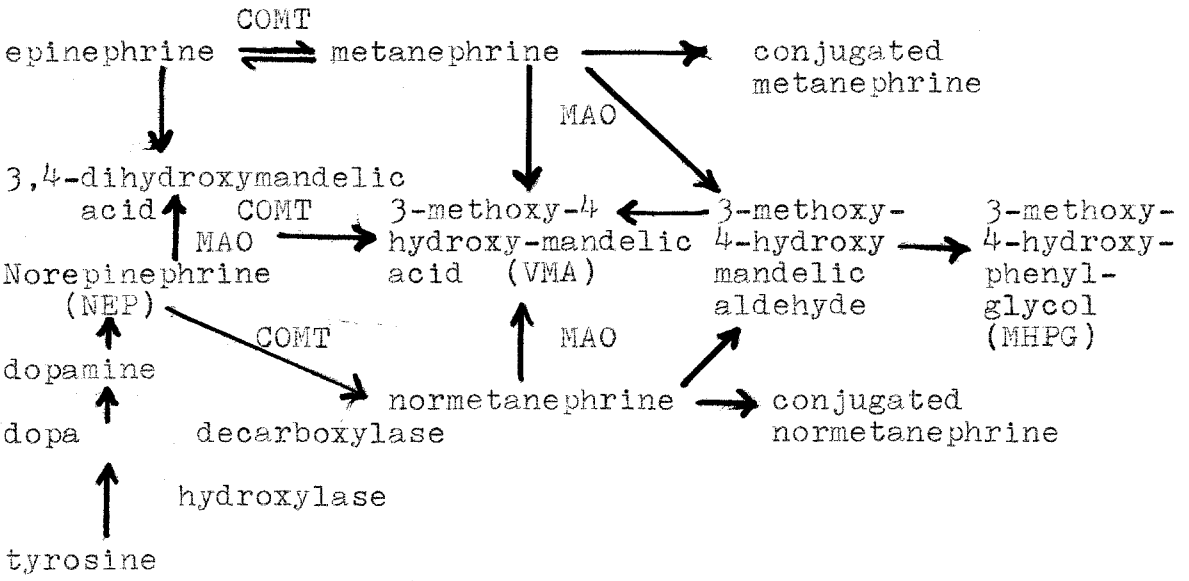
Norepinephrine is a naturally occuring catecholamine located in the central nervous system, the peripheral sympathetic fibers, and in the adrenal medulla. Both biochemical and histochemical methods have demonstrated that norepinephrine (NEP) and the neurohumors, dopamine, and serotonin are concentrated in specific structures throughout the brain ie., the hypothalamus, caudate, and lentiform nuclei. NEP functions as a neurotransmitter substance in the peripheral system. It has been suggested that NEP may function also as one of the central neurotransmitter substances in the brain. NEP is stored in granules in nerve endings and is present in body fluids.

NEP is synthesized from tyrosine with dihydroxyphenylalanine (dopa) and dihydroxyphenylethylamine (dopamine) as the two intermediate steps. More specifically, tyrosine, which is plentiful in the plasma, is hydroxylated to 3,4-dopa which is converted by dopa decarboxylase (aromatic 1 amino acid decarboxylase) to dopamine. This is hydroxylated to form NEP in the granules. The rate limiting step, however, is the tyrosine to dopa step. NEP is being continuously synthesized and broken down, stored and released, and various storage pools are in dynamic equilibrium.[3]

The breakdown of norepinephrine occurs along at least two known pathways. One involves initial oxidation by monoamine oxidase, and the other involves initial o-methylation by catechol o-methyl transferase.

NEP is metabolized inside the cell by oxidase which converts it to 3-methoxy-4-hydroxy-mandelic acid (VMA) through the intermediate metabolite, 3,4-dihydroxy-mandelic acid. Circulating NEP and NEP released by nerve stimulation are metabolized to VMA by catechol o-methyl transferase through the intermediate metabolite normetanephrine.

Route of Metabolism of Epinephrine and Norepinephrine

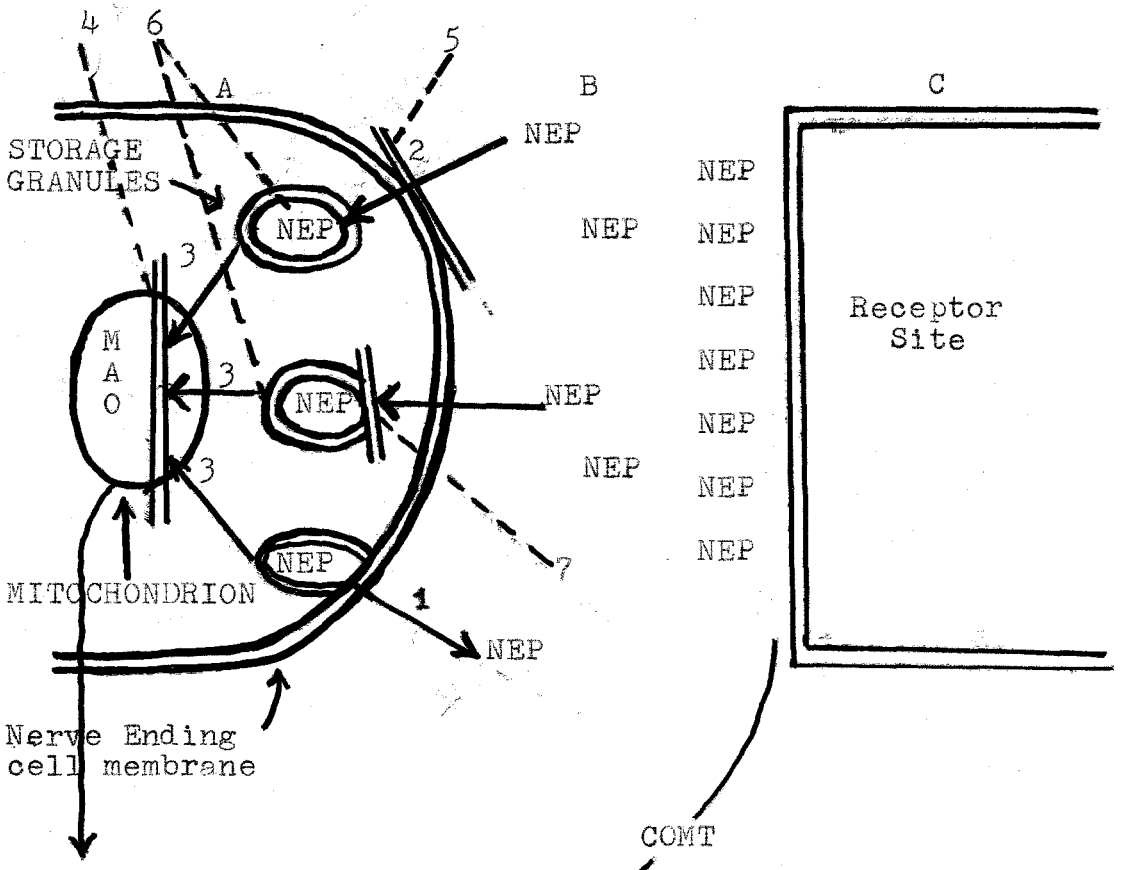


Evidence from a large number of sources suggests that NEP is functionally stored in at least two different pools, a loosely bound and firmly bound pool. Evidence for this is provided by the differential rates of uptake and release of exogenous NEP and the differential release of NEP and various drugs. Of particular relevance to the hypothesis is the suggestion that

reserpine releases mostly NEP from the firmly bound store which is subsequently deaminated to a functionally inactive metabolite. In addition there is a store of NEP which is relatively resistant to the action of reserpine alone, but can be released by electrical nerve stimulation. Both biochemical and histochemical studies indicate that it is difficult to deplete nerves of catecholamines through repeated stimulation.

NEP is thought to be conserved by a process through which the nerve takes up the NEP from the synaptic area and returns it to its stores. The resynthesis and rebinding mechanisms are able to keep up, even with very rapid rates of nerve stimulation. Some investigators suggest that NEP as well as dopamine and serotonin all function directly as transmitter substances while others postulate that one or more of them may act as modulators or regulators of synaptic transmission mediated by some other direct transmitter, for example, ACTH. Inhibition of either rebinding or synthesis results in catecholamine depletion in nerves. The action of catecholamines, released by nerve stimulation is terminated in the synaptic area by rebinding to the cell membrane of the nerve end plate with resultant concentration of NEP within the nerve cell. Intracellular deamination by MAO, within the nerve cell on the other hand, inactivates NEP to VMA and extrudes this inactivated form outside the neuron. Active NEP in the synaptic cleft free of the receptor site is also inactivated to normetanephrine by COMT.[4]

Effect on NEP of Drugs Influencing Depression



(A) noradrenergic nerve ending, (B) synaptic cleft, (1) discharge of NEP into synaptic cleft, (2) reuptake of NEP from synaptic cleft, (3) intracellular release of norepinephrine from storage granules into cytoplasm and on to mitochondricl MAO, (4) MAO inhibitor site, (5) Imipramine and DMI site, (6) methyl dopa site, (7) reserpine site.[5]

The basis of the catecholamine hypothesis of affective disorders is that depressions are thought to be associated with an absolute or relative deficiency of catecholamines in functionally important sites in the

brain, and that elations may be associated with an excess of catecholamines, notably norepinephrine. The postulated pharmacological mechanisms of action of certain drugs give credance to this hypothesis. It has been shown repeatedly that high doses of reserpine markedly depletes NEP from the brain and causes depression in man;lethargy and sedation in animals. The mechanism of action may involve interference with NEP storage in the cytoplasmic granules or at the axonal membrane resulting in either prevention of rebinding or release of NEP from its storage granule into the intracellular sap, thus exposing it to enzymatic attack by MAO. It is then metabolized by intracellular deamination. Methyl dopa depletes brain NEP by acting through its metabolite methylnorepinephrine, which displaces NEP from its storage sites. When conversion of methyl dopa to its metabolites is prevented by the appropropriate decarboxylase inhibitors, methyl dopa has no NEP depleting properties.[6]

Imipramine and desmethylimipramine (DMI) prevents reserpine induced depression by blocking the rebinding or physiological uptake of endogenous NEP at the axonal cell membrane. If NEP is released by nerve stimulation, imipramine acts in such a way as to block the reuptake of this free NEP by the nerve. The MAO inhibitors act by inhibiting the intracellular deamination of NEP, thus increasing the amount available for extrusion to the receptor site.[7]

Lithium salts have been recently well established as effective agents in the treatment of manic and hypomanic states. When administered prophylactically to patients with recurrent depressions, lithium chloride has been reported to decrease the frequency of attacks and to abolish them altogether, just as it does in recurrent mania. In contrast to its well-established direct therapeutic effect in the treatment of the symptomatic phase of mania, however, lithium has little or no direct antidepressant effect when administered during the symptomatic phase of depression. The postulated mechanism of this ion is that of increasing the intraneuronal deamination of NEP thus decreasing the NEP available at adrenergic receptor sites. However, in correlating the clinical effects of lithium with biochemical findings, it is necessary to distinguish the direct therapeutic action of this drug in mania from its prophylactic action in depression, since different mechanisms may be operative.[8]

Summary of the Pharmacological Observations Compatible with the Catecholamine Hypothesis of Affective Disorders.

Drug	Effects in Man	Animal Behavior	Effects on catecholamine in animal brain
Reserpine	sedation depression	sedation	depletion (intracellular deamination)

Tetrabenazine	sedation depression	sedation	depletion (intracel-ular de-amination)
Amphetamine	stimulant	stimulation excitement	Releases NEP onto receptors Inhibits cell uptake of NEP
MAO inhibitors	antidepressant	excitement prevents and reverses reserpine induced sedation	increases levels
Lithium salts	treatment of mania		increases intra-cellular de-amination of NEP--decreases NEP at receptors
Alpha-methyl paratyrosine	sedation (trans-ient) with hypomania upon withdrawl	sedation in some studies	inhibits synthesis
Imipramine	antidepressant	prevents reserpine induced sedation, potentiation of amphetamine effects	inhibits cellular uptake of NEP potentiates action of NEP at periphery

Urinary excretion patterns have also contributed confirmatory evidence in favor of the catecholamine hypothesis. Urinary excretion of normetanephrine which may reflect noradrenergic activity, showed a gradual increase during the period of definitive clinical improvement in depressed patients treated with imipramine. These findings suggest that noradrenergic activity may gradually increase during clinical improvement from depression, and that noradrenergic activity may be relatively decreased in retarded depression and increased in mania.[10] In another study by Maas, Fawcett, and DeKirmenjian using carbon labeled NEP injected into the lateral ventricle of a cat, it was shown that a significant fraction of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) is derived from the brain pool of NEP while urinary 3-methoxy-4-hydroxymandelic acid, metanephrine, and perhaps normetanephrine, reflect catecholamine metabolism in peripheral adrenergic tissues. It was noted that little normetanephrine enters the body pool from the brain and that urinary levels of NEP principally reflect the metabolism of NEP by tissues other than the brain. This study suggests that a significant fraction of (MHPG) is derived from the brain pool of NEP, while VMA metanephrine and normetanephrine reflect catecholamine metabolism in peripheral adrenergic tissue. In support of the catecholamine hypothesis was the fact that there were no statistically significant differences between patients and control groups for levels of metanephrine

or normetanephrine in urine. It was found that the group of depressed patients had significantly lower levels of (MHPG) in urine than did the control subjects.[11]

Steroid, Carbohydrate and Electrolyte Metabolism in Depression

In a study by Curtis, Cleghorn, and Sourkes, a correlation was found between urinary excretion of adrenaline and noradrenaline. The data suggest that in affective states of depression, noradrenalin is excreted preferentially in comparison with adrenaline and corticoids, while corticoids are excreted preferentially in states of anxiety, in subjects whose difficulties were disorders of thinking or behavior.[12] Results of oral glucose tolerance tests in a study by Herzberg, Copper, and Marks revealed no significant difference between the fasting levels of the patients when depressed and on recovery.[13]

The Use of Lithium Carbonate

Nineteen years of clinical experience have shown lithium salts to be effective therapy for acute manic attacks and more recent evidence suggests that it can prevent recurrent psychotic depressive or manic episodes. Lithium's effectiveness was first observed in 1949, by John F. Cade, who noted that guinea pigs given lithium carbonate became sleepy and lethargic.[14] He then

tried the compound on ten manic patients and found that it caused their excitement to disappear. Its action in acute mania has been confirmed in controlled studies by Schou, Gershon, Yuwiler, and Maggs. Lithium was found to be specific in that it removes the hyperactivity and elation without interfering with normal processes.[15] Since the work of Cade, there have been a number of articles in the world literature from Australia, Denmark, England, France, and Russia concerning the use of lithium for the treatment of manic behavior.[16] Of these, the enthusiastic Scandinavian report by Professor Schou, 1959, reviewing ten years of lithium therapy, endeavors to proclaim its epochal character. Kingston from Canada, and particularly Gershon and Yuwiler, an Australian-American team, gave it a most notable introduction to North America in 1960.[17] Despite its well-demonstrated usefulness, lithium has not been much studied or used in the United States. This is due in part to the bad name that lithium chloride developed in 1949 when it was used as a salt substitute for cardiac patients, a use that led to several deaths from lithium poisoning. The introduction of tranquilizers probably further pushed lithium into obscurity in this country.[18]

Reports on Manic Patients Treated with Lithium and Given No Other Physical Therapy

Author	Total	Improved	Unimproved
Cade (1949)	10	10	0
Despinoy and de Romeuf (1951)	3	3	0
Noack and Trautner (1951)	27	26	1
Reyss-Brion and Grambert (1951)	4	3	1
Deschamps and Denis (1952)	4	4	0
Duc and Maurel (1953)	4	3	1
Givstino (1953)	2	0	2
Glesinger (1954)	21	15	6
Schou and associates (1955)	48	39	9
Sivadon and Charoit (1955)	10	10	0
Tevlie and associates (1955)	25	20	5
Gershon and Trautner (1956)	10	9	1
Ric (1956)	37	34	3
Andreani and associates (1958)	14	13	1
Belling (1959)	32	24	8
Schou (1959)	119	91	28
Kingstone (1960)	17	16	1
Hartigan (1963)	45	32	13
	432	352	80

In a study by Schagenhauf, Tupin, and White, lithium carbonate was used in the treatment of ten hospitalized patients with acute, severe manic excitement. Patients were given 300 mg. four times daily until improvement or side effects were apparent. Patients were maintained on 0.6 to 1.2 gm of lithium carbonate daily in divided

doses. The serum levels never exceeded 1.5m eq/L and usually were below 1.0m eq/L. As suggested by other investigators, additional NaCl was given because when given to humans, lithium causes a sodium diuresis which results in a temporary hyponatremia. All the patients aged 21-59, seven females and three males, had a favorable response to lithium therapy. Most had failed to respond satisfactorily to previous intense phenothiazine therapy. Improvement was noted usually on the fourth or fifth day of treatment and always before the tenth day. Excitement, irritability, and euphoria gave way to more appropriate and less irritable affective state, a decreased rate of speech and stream of thought, and decreased psychomotor activity. In this study no attempt was made to correlate serum lithium level and clinical improvement or toxicity. None of the patients experienced any recurrence of manic illness or depressive symptoms as long as he was remained on maintainence therapy. Of three patients who stopped taking a maintainence dose, two promptly went into acute manic excitement in fourteen days.

There is evidence that in addition to controlling symptoms, one of the great values of lithium therapy is its capacity to prevent recurrences of either manic or depressive symptoms when used for extended periods of time on maintainence dosages. Hartigan[20] reported that he had maintained patients on dosages of lithium without an effect for up to six years. This study

suggested the use of lithium for learning more of the nature of manic depressive disorders.[21]

In a study at the New York State Psychiatric Institute by Warton and Fieve, a total of nineteen patients with manic-depressive psychosis, manic phase were treated with lithium between 1959 and 1965. The patients selected for treatment manifested hyperactivity, pressure of speech, and elation state.[22]

Psychiatric History of 19 Patients

Prior manic attacks	Males	Females
one	2	2
two to five	6	7
six to nine	0	0
ten or more	1	1
Prior treatment		
Electroconvulsive therapy		
Improved	2	1
Not improved	0	2
Phenothiazines		
Improved	1	4
Not improved	7	5
Allergic	1	1

After an observation period of ten days, the patients were treated with lithium carbonate for a two-week period at a dosage that maintained the blood level between 1-2 meg./liter. After this period, a maintaince level of 0.5 to 1.0 meg./liter was utilized. The dosage was tapered from 1800 mg./day to 900 mg./day after maintainence levels were achieved. Careful monitoring of blood levels was done to prevent known toxic effects. These have been elaborated by Schou,[23]

Gershon, and Maggs and include gastrointestinal upset, tremor, ataxia, dizziness, decreased blood pressure, and rarely, epileptiform seizures. At high levels in vitro, lithium may block carbohydrate and amino acid metabolism by affecting specific enzyme systems; at high levels in tissue culture, lithium may affect astrocyte metabolism.[24] No information is available as to lithium's action at these doses in man.

In the 25 trials on 19 patients responses were separated into four categories: good response, equivocal response, inadequate trial, and poor response.

Manic Attacks in 19 Patients Treated With Lithium Carbonate

Quality of Response	Number of Trials
Good	11
Equivocal	6
Inadequate	3
Poor	5

An attack was considered aborted when a significant change was noted in all three parameters under observation, ie., decreased motor hyperactivity, altered mood, and decreased pressure of speech. The prognosis and natural history of the individual manic attack are uncertain. Strecker comments that "between ages 15 and 25, the average duration is three to six months with future attacks in general of greater length". Noyes and Kolb state the "average duration of the attack is

six months." Arieti comments that "the prognosis is almost always good, but uncertain as to recurrence." In this study the shortening of the duration of the attack was used as the measure of efficacy and an unequivocal and conservative 44 percent improvement after two weeks on lithium was noted. If the equivocal response group were included, 17 out of 25 (68 percent) improved. Maggs used intensity of the symptoms of the attack as measured by the Wittenborn scale to evaluate the effects of lithium treatment; he reported his results as statistically significant compared with placebo in 18 out of 28 patients treated. Schou, in his data, demonstrated decreased frequency of attacks as well as the capacity to abort attacks in 39 of 48 patients treated or approximately 80 percent improvement including both his "positive effect" groups and "possible effect" groups.[25]

The impression of these investigators was that a closer correlation between observable body activity, social behavior, mood, speech, and metabolism would be needed to further evaluate the effects of lithium. They noted that the reports by Gibbons[26] and Coppen of increased exchangeable sodium and ionic shifts as well as changes in electrophysiology as primary biochemical lesion or epiphenomena remains open to question.

Lithium-Mechanistic Speculations

The site of action of lithium has been suggested as at the thalamic and reticular level,[27] but this

ignores any relevance to the replacement of other anions within the cells by lithium. It is postulated that the curative action of lithium may be the result of its intervening to reduce free energy change, through potassium or sodium displacement by lithium. It may act through enzyme inhibition of ATP energy production and serve to recover lost hormonal control and direction of energy thus preventing an uncontrolled production of free energy in muscle. Lithium could be replacing intracellular fluid sodium, the loss of which helps to stabilize hormonal control of fluid secretion that otherwise fluctuates in periodic illness, the patient being usually polyuric at the beginning of a manic attack and oliguric during depression.[28] Two reports seem related to such possibilities: the observation of Batycharya that the action of lithium is similar to the action of insulin in promoting a rapid uptake of glucose from extracellular fluid into the cell, and the observation of Carr and Soller that lithium has a very large electro-osmotic effect on water transportation in macrocellular experimental models and probably also in true mosaics.[29]

In a review of pending biochemical questions of lithium therapy, Greenspan (1968) cited several areas of observation. His studies demonstrated that in depression there is an increase in sodium retention compared with the recovered state. This is paralleled by an increase in 17-hydroxycorticosteroid and 17-ketosteroid levels. Such elevations were not usually

observed in manic patients. Studies of sodium distribution and 24-hour exchangeable sodium in manic and depressed patients who responded to lithium revealed an increased 24-hour exchangeable sodium in depression.[30]

Overton (1902) noted that if sodium were removed from the bath surrounding frog muscle it would no longer respond to electrical stimulation. Lithium was the only ion substituted for sodium that restored the muscle's excitability. Keynes and Swan (1959) demonstrated in vitro that lithium moves into muscle fibers like sodium, but does not leave as readily. Moreover, the egress of lithium was not blocked by removal of potassium which suggests that sodium and lithium entered alike but did not share the same pump mechanism for extrusion. It was found that lithium accumulated within muscle fiber and eventually rendered it inexcitable. Zerahn (1955) found that lithium was actively pumped across frog skin, but unlike sodium, accumulated in the epithelium. Similar findings were noted in isolated nerve observations but most of these were done with high concentration of lithium in vitro. The implication is, however, that the action of lithium may be due to its effect upon sodium metabolism.[31]

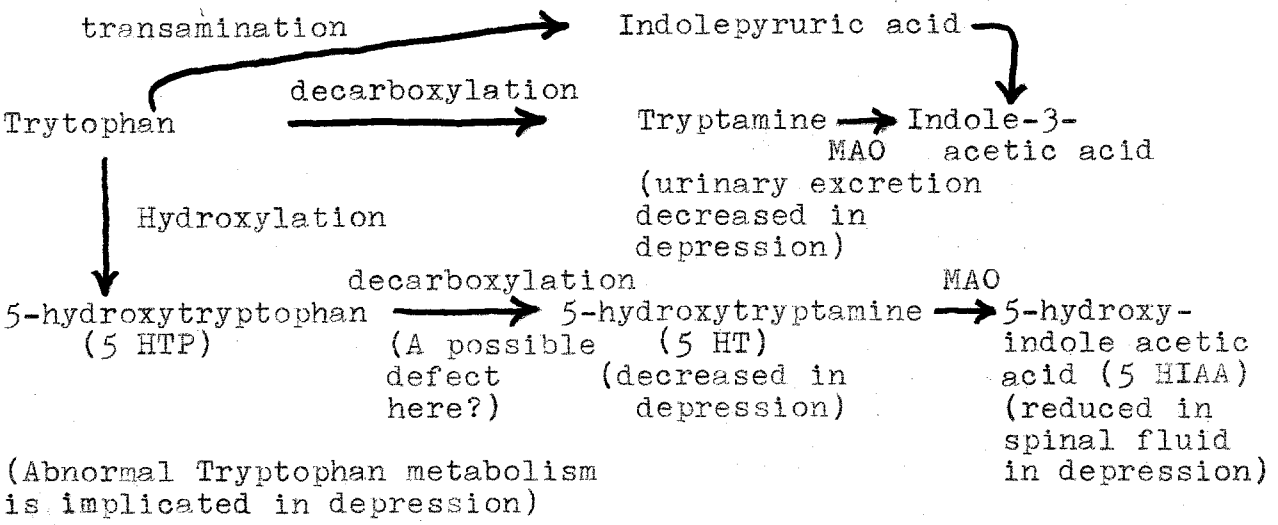
One of the most consistent findings has been that of an increase of 50% in the amount of intracellular sodium together with a small but unknown amount of exchangeable bone sodium. This was found to return to normal after recovery (Coppen, 1963). Low concentrations of intra-

cellular potassium were found in depressed patients, but this did not alter with clinical improvement (Shaw, Coppen, 1956). These changes are for body electrolytes as a whole, and there is no direct evidence that parallell changes take place in the central nervous system. If camparable events did occur in the brain, cerebral excitability would be much affected by reduction of both resting and action potentials (Shaw, Coppen, 1966). In addition to these changes in electrolyte distribution, a reduction in extracellular water in depression has been observed in investigations using either the thiocyanate space or the volume of radioactive bromine. In mania, distribution studies have revealed similar (but greater) changes in the distribution of sodium compared with those found in depression; the average being twice normal.[32]

Tryptamine Metabolism in Depression

Coppen, Shaw, and Farrel (1963) showed that large doses of DL- tryptophan (214 mg./kg. body weight) given to depressed patients receiving tranylcypromine (a MAO inhibitor) potentiated the anti-depressive effects of the drug. This also increased the level of 5-hydroxytryptamine (5HT) and tryptamine in the rat.

Metabolic Pathways Investigated



In an initial investigation by Coppen, Shaw and Malleson, (1965) the rate of decarboxylation of 5-hydroxytryptophan (5 HTP) was studied by measuring the expiratory rate of $^{14}CO_2$ following the injection of 5 HTP labelled with ^{14}C in the carboxyl group. The results showed that the rate of expiration of $^{14}CO_2$ was reduced during depression, probably because of a slower rate of decarboxylation of 5 HTP to form 5 HT. In a carefully controlled study by Coppen, Shaw, Malleson, Eccleston, and Gundy (1965) tryptamine and IAA excretion was investigated in 13 severely depressed patients before and after recovery from their illness. Urinary tryptamine excretion was found to be abnormally low during the illness and rose by an average of 70% to approximately normal values after recovery. Urinary IAA showed no significant change. The findings were not related to urinary pH and volume, nor to diet.

Plasma tryptophan levels did not vary significantly. Unexpectedly, intravenous tryptamine given to depressed patients receiving MAO inhibitors showed that this procedure, unlike that with tryptophan, had no therapeutic effect. One explanation for this discrepancy was that tryptamine is inert in man or that a species difference in the blood-brain barrier exists between man and the smaller animals. 5-HTP, which passes the blood-brain barrier and reverses reserpine depression in small laboratory animals (Hess and Doepfner, 1961) also has little or no antidepressive action in man (Kline, Sacks, and Simpson, 1964).[33] 5-HT and tryptamine are produced in the brain only from tryptophan, the most likely normal precursor of these amines in the CNS.

An Alternative to the Catecholamine Hypothesis?

The studies of Dewhurst and Marley (1964) with particular reference to the use of the young chick concluded that cerebral amines fall into two main functional groups. Excitant (Type A) amines have the general formula R. CH_2, CH_2, NH_2, where R is a fat-soluble and planar hydrocarbon (e.g., indolyl or phenyl). All amines of this group produce all the phenomena of the alert state both behaviorally and physiologically with tryptamine being the most potent physiological agonist. Depressant (Type C) amines

are of the general structure R^1. CH(OH). CH_2. NH. CH_3, where R^1 is water soluble (e.g., catechol). Such amines produce all the phenomena of drowsiness or sleep, adrenaline being the most potent physiologic agent. Type A (excitant) or type C (depressant) activity depends primarily on lipid solubility and not on whether a substance is an indole or catechol or phenylethylamine. Dewhurst and Marley found that type A amines act through a specific receptor identical to the peripheral tryptamine receptor; type C amines are mediated by a receptor similar to the peripheral alpha receptor. Thus, the known alerting effect of catecholamines has been shown to depend on hypertensive responses secondary to stimulation of peripheral alpha receptors. It has also been shown that a small group of amines (type B), which includes 5 HT, are biphasic, having the ability to act on both A and C receptors sequentially. Depressions, thus are related to a deficiency of type A amines or malfunctions of the A receptor, whereas in mania the converse would be true.[34]

Objections to this hypothesis were raised by H. Weil-Malherbe of N.I.M.H. He states that Dewhurst's view of depressive psychosis is due to a deficiency of "type A" amines, presumably tryptamine, and it must be inferred that tryptamine, has a role as a nervous transmitter. To substantiate this it would be necessary to show that tryptamine, has been found in the normal brain; only small amounts were found after combined

administration of L-tryptophan and MAO inhibitors.[35]

The current concept of the alerting effect of brain catecholamines is based on the effects of dopa and dexamphetamine. Dopa, which crosses the blood-brain barrier, is supposed to act as a precursor of brain dopamine and NEP; the action of amphetamine is also assumed to be indirect and mediated by dopamine and NEP. Dewhurst proposes a direct action for dopa and amphetamine. In doing so he overlooks the following; (1) the dopa effect is potentiated by MAO inhibitors and blocked by decarboxylase inhibitors (Carlsson, Lindquist, Magnusson, 1957); also, the alerting effect of a series of related amino acids is correlated with their rate of decarboxylation (Blascho and Chrusciel, 1960): (2) the central action of amphetamine is blocked when catecholamine synthesis is inhibited (Randnup, 1966). Similarly, the antidepressive action of impramine has been shown to depend on a well-stocked store and normal synthesis of brain catecholamines (Sulser, Soroko, 1965). Whether the alerting effects of epinephrine and NEP are purely of peripheral origin is still controversial (Dell, 1960).[35]

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