Presidential Address

Metabolism and Mentation¹,²

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ABSTRACT. The ultimate supreme function of the body is mentation; the other portions of the body are subservient to it. Dysmentation is very common, highly distressing, and enormously expensive. All abnormalities in mentation are presumably associated with altered metabolism. Dysmetabolism causes dysmentation and vice versa. Altered cerebral metabolism is produced by primary or secondary cerebral disorders in the body, and by extracorporeal influences—abnormalities in diet, climate, social status, and numerous other environmental factors; there frequently is a polycyclic interplay of influences. Dysmentation is often found in many genetic disorders, hyper- and hypoparathyroidism, hyper- and hypoadrenocorticism, and hypothyroidism. There are indications that it also occurs frequently in many other endocrine and metabolic disorders, but data are inadequate. Many neurotransmitters have been described, including especially acetylcholine, norepinephrine, dopamine and serotonin. Abnormalities in the metabolism of one or more of these have been reported in various types of dysmentation. In mental depression and mania there are abnormalities in catecholamine metabolism, with lesser changes in serotonin. Certain observations have suggested abnormalities in serotonin metabolism in schizophrenia, but data remain inadequate. Hallucinations and other marked behavioral changes have accompanied altered serotonin metabolism and/or ingestion of serotonin-like compounds. Changes in acetylcholine levels have produced anger, rage, anxiety and other behavioral states. Sleep seems to be associated with increased serotonin and decreased catecholamine levels; insomnia accompanies the reverse. Learning and memory are influenced by the metabolism of protein, nucleotides, carbohydrate, fat, vitamins, minerals, and numerous other factors. The brain has richer contents of adenosine-3',5'-phosphate, adenylyl cyclase and phosphodiesterase than any other organ, but relatively little is known about the functions there of this nucleotide. As endocrinologists and metabolists, problems of dysmentation confront us as highly interesting, and probably richly rewarding areas for research, teaching and practice. (J Clin Endocr 31: 461, 1970)
TABLE 1. Genetic disorders with dysmentation (dysmentation in >75%)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiologic enzyme deficiency</th>
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<tbody>
<tr>
<td>Albright’s hereditary osteodystrophy</td>
<td>Hydrocephalus, X-linked</td>
</tr>
<tr>
<td>Andersen’s disease</td>
<td>Hypercalcemia, infantile</td>
</tr>
<tr>
<td>Apert’s syndrome</td>
<td>Krabbe’s disease</td>
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<tr>
<td>Berardinelli’s lipodystrophy</td>
<td>Laurence-Moon-Biedl syndrome</td>
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<tr>
<td>Carpenter’s syndrome</td>
<td>Lowe’s disease</td>
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<tr>
<td>Cerebral gigantism</td>
<td>Marinoso-Sjogren syndrome</td>
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<tr>
<td>Cerebro-hepato-renal disease</td>
<td>Myotonic dystrophy</td>
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<tr>
<td>Clouston ectodermal dysplasia</td>
<td>Prader-Willi syndrome</td>
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<tr>
<td>Cockayne’s syndrome</td>
<td>Rubinstein-Taybi syndrome</td>
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<tr>
<td>Cornelia de Lange syndrome</td>
<td>Sanfilippo’s syndrome</td>
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<tr>
<td>“Cri du chat” syndrome</td>
<td>Seckel’s syndrome</td>
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<tr>
<td>Deletion of long arm of chromosome 18</td>
<td>Sjogren-Larsson syndrome</td>
</tr>
<tr>
<td>Deletion of short arm of chromosome 4</td>
<td>Smith-Lemli-Opitz syndrome</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>Tay-Sachs disease</td>
</tr>
<tr>
<td>Generalized gangliosidosis</td>
<td>Trisomy 13</td>
</tr>
<tr>
<td>Hunter’s syndrome</td>
<td>Trisomy 18</td>
</tr>
<tr>
<td>Hunter’s syndrome</td>
<td>XXXXY syndrome</td>
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Examples of Disorders Associated with Dysmentation

Genetic disorders. Dysmentation is being discovered, with rapidly increasing frequency, to be associated with many different genetic disorders (2–4); mental retardation is common. In Tables 1 and 2 are...
listed disorders with a high incidence of dysmentation. A defect in the activity of almost any enzyme involved in amino acid metabolism may be associated with mental retardation (2, 3). All the primary overflow aminoacidurias, with the possible exception of tyrosinosis, are associated with brain damage. Mental retardation occurs in most patients with no-threshold aminoacidurias, and in three of the five renal aminoacidurias. Hundreds of different mutations may lead to various alterations in enzyme activity. However, it is not to be expected that in all instances there is a decrease in intelligence. For example, superior intelligence has been reported in association with retinoblastoma, hyperuricemia, siblings of patients with phenylketonuria and parents of subjects with child autism (4).

That an enzyme defect can lead to marked behavioral changes is well illustrated by the Lesch-Nyhan syndrome (5). This genetic disorder of purine metabolism leads to marked mental retardation, and aggressive-compulsive self-mutilative behavior, such as extensive chewing off of the lips, the fingers, and other areas; it also causes spastic cerebral palsy and choreathetosis. Another such instance of a single enzyme defect causing marked mental abnormalities is phenylketonuria. This abnormality can also be produced in children not having the enzyme defect through placental transmission of substances, such as phenylalanine, from the afflicted mother. Reductions in the level of phenylalanine decrease progression of the disease. Likewise, in galactosemia, galactose can be removed from the diet with great benefit. In orotic aciduria, the feeding of cytidylic and uridylic acids offers distinct advantages.

The rapidly increasing use of amniocentesis is proving of great aid, particularly with the increase in liberalization of abortion laws. Thousands of amniocenteses have been performed with minimal maternal and fetal mortality (6, 7). Numerous conditions can be diagnosed by this procedure and they can be managed appropriately by means of abortion. A very good example is Down's syndrome, which occurs in approximately 2% of the offspring of mothers who are more than 40 years of age.

**Endocrinopathies and Dysmentation**

Although we have searched the literature extensively for the incidence and types of dysmentation associated with endocrinopathies, we have been keenly disappointed with the results. In most of the reports, either there have been too few cases analyzed or inadequate definition of the type of dysmentation, lack of control studies, failure of identifying whether the dysmentation was produced by the endocrinopathy and/or corrected with its cure. Moreover, in the reports there is tremendous variation in the incidence of dysmentation in endocrinopathies. For example, in some dealing with Cushing's disease, an incidence of dysmentation is found in more than 75%, whereas in certain papers dealing supposedly with all the manifestations of the disease, there is no mention of this aspect. Despite numerous disappointing features found in the literature, we are presenting some of the results with the objective of stimulating much more research in these areas. Our samples deal predomi-
In a study of ten of 11 patients in one family with hyperparathyroidism and in ten members with no evidence of endocrine disease, it was found that eight of the ten with the hyperparathyroidism had experienced major psychiatric symptoms for a prolonged period, whereas, among those without hyperparathyroidism, psychiatric difficulty was found in only one (9).

Dysmentation has been reported (10) in 89% of patients with primary hypoparathyroidism and in 98% of those with postoperative hypoparathyroidism (Fig. 2). The patients designated as having organic brain syndrome had major emotional disturbances with impaired intellect. In those with functional psychoses, some displayed schizoid changes. Other features were irritability, emotional alteration, impaired memory, and mental confusion; some had depression. Features exhibited by the neurotic group included such things as obsessions and phobias. Calcium therapy caused marked amelioration in the symptomatology of individuals with hypoparathyroidism, but permanent dysmentation persisted in some. It is known that the calcium deposits and other structural changes in the brain may continue to exist in some patients. It is not surprising that there should
be severe alteration in mentation with either marked hypercalcemia or hypocalcemia in view of the highly important role of calcium in cell membrane permeability, enzyme functions, nerve transmission and in other ways.

**Adrenal dysfunction.** In Cushing’s disease, some authors (11-14) have reported moderate or severe mental changes in approximately 50% (Fig. 3). The commonest type of mental alteration is depression; schizoid manifestations are found in many. Whereas some patients experience dramatic amelioration in the dysmentation post adrenalectomy, others continue with it. However, many factors must be considered in analyzing the basis for the persistence of dysmentation. Among these are: (a) damages in the brain from prolonged hyperglucocorticosteroidism, (b) failure of replacement glucocorticoid therapy to reproduce the variable levels of glucocorticoid found in normals, (c) persistence of hyperadrenocorticotropinism post adrenalectomy, (d) alterations in personality reactions from severe and/or chronic hyperglucocorticosteroidism to a degree that normal readjustments do not take place, and (e) the likelihood that some patients had intracerebral abnormalities preceding the Cushing’s syndrome. Indeed, it has been proposed (15) that Cushing’s disease may be a psychosomatic disturbance occurring as a psychophysiological response to bereavement or its emotional equivalent, occurring in predisposed individuals with a disturbance in the hypothalamic-pituitary regulation of adrenocortical activity. The concept is further emphasized by the observation that some of the patients studied intensively had a history of significant emotional disturbances preceding the onset of hypercorticism. In this connection, of course, it must be mentioned that not uncommonly Cushing’s disease has a very insidious onset, extending over a period of 20 years or more before being diagnosed, making it difficult to date the onset of the disease. Moreover, it is conceivable that a number of disturbances not produced by hypercorticosteroidism occur. In many patients there is a
FIG. 4. In 4 series (17–20) of studies of patients with Addison’s disease, significant mental abnormalities were found in more than 50%.

hyperadrenocorticotropic hormone and most probably an increase in the ACTH releasing factor from the hypothalamus. In turn, there are probably alterations in other parts of the brain which affect the hypothalamus in this way. Therefore, even with the personality changes preceding the hypercorticism, it seems possible that there is intracerebral disease which most likely would be of intrinsic origin, although extrinsic factors may have important influences, especially since it is known that in stressful situations an increase in the RF-ACTH-corticosteroid cycle occurs. It is also known that glucosteroids induce a large number of biochemical reactions throughout the body, including the brain (16), and that they induce personality changes to the extent of frank psychosis in certain individuals.

Addison’s disease was found in four reports (17–20) to be associated with mental abnormalities in more than 50% of the patients (Fig. 4). The mental disorders include a variety of neurotic traits, depression, and paranoid psychosis. In most patients there is a dramatic improvement with appropriate corticosteroid therapy.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
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<tbody>
<tr>
<td>Mental slowness</td>
<td>93</td>
</tr>
<tr>
<td>Subnormal memory</td>
<td>65</td>
</tr>
<tr>
<td>Subnormal learning</td>
<td>53</td>
</tr>
<tr>
<td>Delusions</td>
<td>39</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>37</td>
</tr>
<tr>
<td>Insanity</td>
<td>36</td>
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</table>

Myxedema. One of the best studies dealing with the symptomatology of myxedema was published in 1888 (21). As seen in Table 3, most of 109 unselected cases of myxedema had alterations in mentation. Particularly prominent was impairment of learning and memory, but there also were many who were bothered by delusions and hallucinations, and approximately ⅓ were designated as insane. Most of these features are reversed by appropriate thyroid hormone therapy. This therapy has been found to be of distinct advantage in depression with hypothyroidism and also in a number of patients with euthyroidism (22). With early diagnosis of myxedema, dysmentation is less common.

Other endocrinopathies. Almost all patients with insulinoma have at some time impairment of mentation. With acute severe hypoglycemic episodes there may be anxiety, bizarre behavior, and mental confusion, which may progress to coma, with or without permanent brain damage (23). In addition to these acute episodes, one of us (R. H. Williams) has observed in most of his insulinoma patients chronic personality changes, not uncommonly extending over a period of many years. The pattern has been that of depression, bizarre behavior, sometimes schizophrenia, anxiety and other psychoneurotic manifestations. Although many of these manifestations disappear after removal of insulinoma, some persist, with gross brain damage attributable to severe hypoglycemia.

Unfortunately, we have been unsuccess-
ful in obtaining adequate information concerning the incidence and types of dysmenorrhea with other endocrinopathies. However, there are some indications in the literature that there is an increase in mental disorders in association with acromegaly, panhypopituitarism, gonadal insufficiency, thyrotoxicosis, diabetes, pheochromocytoma, and carcinoid. This is in accordance with our own experience.

**Mental Depression and Mania**

A large variety of endocrinopathies and other metabolic disorders are associated with mental depression, and often the depression is ameliorated with correction of metabolic abnormalities. Disorders in catecholamine or corticosteroid activities have been often associated with depression. Reserpine and other drugs that decrease brain norepinephrine and serotonin tend to cause depression. Drugs causing improvement in depression increase these amines. This includes especially the MAO inhibitors (e.g., hydrazines and nonhydrazines), tricyclic compounds (e.g., imipramine), L-DOPA, amphetamines, and phenothiazines (24–26). The improvement that is found with thyroid hormone therapy presumably is related to its synergistic action with catecholamine (22).

Many depressed patients have been found to have hypernormal levels of serum and urinary 17-hydroxycorticosteroids, the elevation being greater in the serum (27). Certain ones have also been reported to have disturbed diurnal rhythm and resistance to dexamethasone depression; the changes disappeared with successful management of depression (28). Some depressed patients do not have the increased corticosteroid levels but on the contrary actually have subnormal levels (29).

The amount of cyclic AMP excreted in the urine usually is subnormal in depression and hypernormal with mania. In each instance, there is a tendency for cyclic AMP to return to normal with correction of the mental disturbance (30).

In mania, there are increases in cerebral norepinephrine and serotonin. It is benefited by drugs that lower the levels of these compounds. Lithium benefits mania to a significant degree (31). However, it sometimes has benefit in depression.

**Schizophrenia**

Schizophrenic reactions have been found in approximately 60% of patients in mental hospitals and in as many as 50% of admissions to some adult psychiatric clinics (32). Many different studies have indicated that genetic disorders constitute a prominent etiologic role. Monozygotic twins have concordance for schizophrenia four times greater than dizygotic (32). Among monozygotic twins with one member showing schizophrenia, the second one exhibits this in 46% of the instances. Moreover, most of the remaining 54% have been found mentally abnormal. Apparently all the abnormal, although nonschizophrenic, co-twins have been found schizoid—with only 13% having been judged normal or near normal (33). Moreover, when both parents have been found schizophrenic, an estimated 66% of their children have been found schizophrenic. Among children born of schizophrenic mothers who were reared from the age of approximately one month in adoptive or foster homes, in comparison with similar adopted children born to normal parents, there was a several-fold larger incidence of schizophrenia, mental deficiency, antisocial personality, involvement in crime, and commitment in psychiatric institutions. About 45% of the

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5 Abbreviations: ACH, acetylcholine; c-AMP, adenosine 3',5'-phosphate; CNS, central nervous system; DA, dopamine; DOPA, dihydroxyphenylalanine; EPI, epinephrine; 5-HT, 5-hydroxytryptamine (serotonin); 5-HTP, 5-hydroxytryptophan; GABA, T-aminobutyric acid; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PKU, phenylketonuria; REM rapid eye movement.
siblings, parents and children of a schizophrenic patient are schizoid or schizophrenic. Many other reports (32) show the high incidence of genetic transmission of schizophrenia. However, environmental and other influences are also important in the development of this disease (34).

There have been many reports of neurochemical disorders in schizophrenia. Many of the psychomimetic compounds which do not upset consciousness are chemically related to norepinephrine, dopamine, and serotonin. Indeed, they are chiefly methylated derivatives of these compounds. Much has been written concerning the increase in methylated catecholamines and methylated indoleamines as being the basis of schizophrenic reactions, but information remains inadequate to substantiate this. Schizophrenic-type patterns have been produced by LSD, mescaline, hypoglycemia, adrenal disorders, and a large variety of other drugs and diseases. In the light of the present information, it seems best to regard schizophrenia as a characteristic type of syndrome with polyetiologies.

Learning and Memory

Numerous compounds affect learning and memory, e.g., cholinergics, catecholamines, and ones which affect protein and RNA synthesis. Increases in acetylcholine in the synapses decrease synaptic transmission, which in turn can lead to amnesia. Synthesis of protein and RNA synthesis are not required for short-term memory; it is associated with electrical changes in the synapses. With long-term memory there are increases in protein and RNA synthesis occurring shortly after learning (35–38). Glassman (39) has stated that, although RNA and protein synthesis might be involved in memory, such synthesis is not a direct requirement but may be associated simultaneously with other functions in the nerves. Some soluble proteins are unique to the brain. They are highly acidic, e.g., they may contain as much as 30% glutamic acid. Possibly they influence DNA activity by blocking histone by combining with it. The injection of brain extract or of RNA from trained rats into untrained ones facilitates learning. One such compound has 14 amino acids. The hippocampus is one of the structures involved in learning and short-term memory (36). The mammillary bodies, thalamic dorsomedial nucleus, and medial portion of the pulvinar are involved in long-term memory. Extensive lesions in the frontal lobe do not seem to influence significantly this memory. Relatively little is known regarding the coordinated storage and retrieval of knowledge.

Sleep

Sleep is very much influenced by serotonin, catecholamines, glucosteroids, thyroid hormones and numerous other compounds as well as by nerve structure and many environmental factors. Moreover, there are distinct differences in the stages of sleep and the influence of factors upon these levels of sleep. Stage 1 consists of low-amplitude, fast-frequency EEG activity; stage 2, low-amplitude, fast-frequency activity; stages 3 and 4, high amplitude, slow-frequency waves (40). Stage 1 is the lightest of the four stages. Stage 2 is heavier; the EEG has lower frequencies and higher amplitude than stage 1. Stage 3 has waves of lower frequencies and higher amplitude than stage 2. The heaviest sleep is stage 4, with a very slow cycle and waves of high amplitude. The REM period occurs at the end of stage 1. REM sleep occurs only after prolonged non-REM. During REM sleep, neuronal and metabolic activities and autonomic functions such as heart rate, respiration, and blood pressure are at increased levels, often comparable to the waking state. With the REM stage, there is a marked decrease in the tonus of head and neck muscle and the EEG waves are of low amplitude and of fast frequency. This is the period in which dreams are most common, including hallucinatory ones. Dream recall during this stage is reported...
in 80% but not very often found in the other stages of sleep. The normal young adult dreams approximately 1/5 of his eight-hour period of sleep. The REM periods occur periodically throughout the night at intervals of approximately 90 minutes.

In normal sleep, all stages are present and occur during a similar percentage of time in chronological order. The percentage of REM sleep after infancy remains relatively stable through life, whereas total sleep and stage 4 sleep decrease progressively with increase in age. With abnormal sleep, all stages are present, but their percentage distribution and sequence in time is not normal. Normally, the greatest amount of stages 3 and 4 are in the first third of the night, and the greatest amount of stage 1 and REM in the last third, whereas stage 2 is evenly distributed. On the average, the young adult spends 50% of his sleep in stage 2, 20% in stages 3 and 4, and 20 to 25% in stage 1 and REM.

Most sedatives induce abnormal sleep, especially since they decrease the REM sleep. Upon withdrawal, the REM sleep occurs in excess, with increased tendency for nightmares. Amphetamines and catecholamines decrease REM sleep, with compensatory increase in non-REM sleep. Drugs which increase brain 5-HT increase sleep, whereas those that decrease 5-HT may induce a stage of permanent wakefulness. Parachlorophenylalanine can cause marked depletion of serotonin with resulting insomnia and particularly a decrease in the REM sleep. The 5-HT neurons are almost exclusively in the raphé nuclei (41). Destruction of the raphé system causes permanent wakefulness and a decrease of cerebral 5-HT but no change in NE. When 5-HT and NE are both lowered, e.g., by reserpine, both slow and paradoxical sleep disappear very rapidly, and there is a continuous fast cortical EEG, with continuous bursts of ponto-geniculo-occipital spikes, characteristic of paradoxical sleep. Slow-wave sleep appears to be related chiefly to serotonin levels, whereas the paradoxical sleep is related to catecholamine activity.

Slow-wave sleep is characterized by synchronized cortical electrical activity and constitutes about 75% of the total sleep. Paradoxical sleep is associated with fast waves of low voltage, desynchronized cortical activity similar to that found during waking, REM, and disappearance of muscle tone (42). Both these stages of sleep seem to be expressed by some active hypnogenic mechanism, but localization of such structures that inhibit the arousal system has not been found; they appear to be chiefly in the lower brain stem. The slow-wave sleep tends to be associated with the serotonin activity of the raphé system, while norepinephrine in the pontine tegmentum seems to trigger paradoxical sleep (42). During paradoxical sleep, there is a very significant decrease in total glycogen in the subcortex and caudal brain stem (43). Regions of the brain high in 5-HT do not show much evidence of circadian rhythm. Such rhythm is found of greatest amplitude in the frontal cortex, hypothalamus, and lateral lower brain stem (44). Inosine decreases catecholamine activity and increases 5-HT—such apparently being the reason for its capacity to increase sleep. It also increases the production of ammonia (45).

Persons who go without sleep for extended periods frequently exhibit disorders of thought and perception, sometimes indistinguishable from those seen in schizophrenia. Minor psychological changes are observed during the REM sleep deprivation period (46). It appears that a loss of REM sleep necessitates its make up later. Hallucinations and delusions may appear after a week or more of sleep deprivation.

Less total sleep and early morning awakening characterize depression; also, there is often a decrease in stage 4 sleep. However, in normal middle-aged and adolescent subjects, there tends to be a de-
crease in stage 4, but this level is very high in childhood. Schizophrenics have shown relatively few abnormalities of REM sleep.

The reticular system helps maintain wakefulness. If the upper reticular system is destroyed in the region of the posterior hypothalamus, somnolence occurs. Sleep can be induced by stimulation of the thalamus. It can be induced by extensive lesions in the thalamus, hypothalamus, or central reticular formation.

**Neurotransmitters**

The neurotransmitters are chiefly biogenic amines, including NE, DA, 5-HT, ACH, histamine, certain amino acids and polypeptides. Since most of these compounds do not permeate adequately the blood brain barrier, they are synthesized in the brain. The immediate precursors of certain biogenic amines are prevented from entering the CNS by an enzymatic trapping mechanism located in the capillary walls (46). For example, DOPA or 5-HTP is decarboxylated to the corresponding amine in the capillaries. DA and 5-HT are formed in the endothelial cells and pericytes. MAO is active in the capillary endothelium. In the brain, some of the precursor amino acids penetrate in the parenchyma only after previous inhibition of the decarboxylating enzymes. Amino acids are transported across the blood brain barrier by catalytic mechanisms or permeases which are rapid, selective and stereospecific. The permeases are quite nonspecific within groups of amino acids (47). Each amino acid can compete with the others for a given permease. Some of the behavioral alterations which result from PKU, histidinemia, maple sugar urine disease, and branched-chain amino aciduria are associated with altered monoamine levels in brain, because of the competition of the amino acids for the blood brain barrier. Phenylalanine inhibits tryptophan hydroxylation. Certain amino acids can be quite toxic to the brain. Leucine causes severe mental retardation. Tryptophan produces abnormal behavior; phenylalanine and leucine decrease 5-HT but tryptophan increases it. Analogs of acetylcholine or the monoamines may be hallucinogenic and concerned with consciousness and perception. Some nerve fibers respond to some neurotransmitters but not to others. Transmission at most synapses is produced by release of small amounts of transmitter chemicals. Most of the transmitters are stored in presynaptic vesicles of terminal nerve endings, thereby assuring unidirectional synaptic transmission. When released from the presynaptic terminals, most of the neurotransmitters become bound to receptors on postsynaptic membranes of the effector cells. A transient alteration in membrane permeability results, particularly to certain ions. With excitatory transmitters there is increased transmission to Na+ and at least one other ion; the ionic currents depolarize the membrane. With inhibitory transmitters, there is increased permeability to K+ and/or Cl−, resulting in hyperpolarization of the membrane; this inhibits the action of the postsynaptic cell.

After biosynthesis and storage of biogenic amines, there are three active stages in the central monoamine synapses that occur: release, response, and reuptake (48). Desmethylimipramine and chlorpromazine decrease the initial uptake and prolong the disappearance of the labeled amine. They also influence the uptake and release of NE by stimulated nervous tissue. Chlorpromazine decreases DA levels in the striatum. Once the amino acids penetrate the neurons, there may be hydroxylation, decarboxylation or, in the case of DA, beta-oxidation. There then is uptake and storage in membrane-bound granules. Subsequently, the amine may diffuse from the cell, some becoming bound to protein. Interaction with a specific receptor often occurs, initiating a specific physiologic response. There then tends to occur dissociation from the receptor site and termination of the effect, the latter being produced.
generally by one of four methods: enzymatic destruction, reuptake of the amines by the cell, diffusion from the area, or a combination with nonspecific proteins.

In Table 4 are shown sites for the highest concentrations of ACH, DA, NE and 5-HT, their precursors, and principal enzymes involved in their synthesis, and in their degradation. Various workers have demonstrated that during severe stress there is a focal and/or total decrease of one or more amines in the brain. When the amygdala in cats is stimulated, there is a rage response at times, whereas at other times there is sedation or no effect. When rage occurs, there is associated in the telencephalon a marked fall in NE but not in DA. When no rage occurs, there is no change in the amine. ACH, NE, DA and 5-HT activate or inhibit particular cells at various places in the CNS. GABA is predominantly inhibitory. Glutamate and a number of amino acids are predominantly excitatory. ACH action tends to be faster and shorter than that of other amines, such as NE. NE appears to suppress the stimulation offered by ACH. Thus far it has not been shown that the transmitters cause an alteration in behavior by specific local action.

A large number of drugs exert very important influences on behavior by means of altering levels of activities of neurotransmitters (48). For example, as little as 70 μg of LSD can produce acute psychosis with hallucinations, delusions and other psychotic features. Such changes have been visualized as possibly being associated with alterations of 5-HT metabolism. Reserpine causes frank depression. It depletes 5-HT, NE and DA. The changes are rapidly reversed by MAOI plus DOPA. 5-HT has much less effect in reversing these changes. Iproniazid is a euphoric and psychomimetic agent which blocks MAO and increases the levels of 5-HT and of NE. α-Methyl-p-tyrosine blocks catecholamine synthesis specifically, markedly reducing the catecholamines without changing 5-HT levels, thereby producing a sedative effect. p-Chlorophenylalanine blocks tryptophan hydroxylase, thereby decreasing 5-HT and not affecting significantly the NE level. Essentially all drugs with a fairly specific effect on mood in man affect brain NE. Imipramine, one of the most potent antidepressants, increases the levels of catecholamines, acting centrally and peripherally to prevent their reuptake in presynaptic receptors, thereby making more available for the post synapses. Dextroamphetamine seems to increase NE action by way of blocking the reuptake and by increasing the release post synaptically,
thereby decreasing deamination and increasing the methylated form. Euphoria and insomnia often result from amphetamines. Drugs that cause sedation or depression of mood cause intracellular release or destruction of NE, so less is available at the synapse, whereas those that decrease depression and cause euphoria increase the level of NE at the central synapse.

Acetylcholine. The highest levels of ACH in the brain tend to be found in the basal ganglia and mesencephalon (49, 50). There also is a high content in the hypothalamo-neurophyseal tract. It tends to be lowest in the cerebellum and the cerebral cortex. It is likely that in noncholinergic neurons there is an initial release of ACH by the nerve impulse to promote the secondary release of another neurohumoral transmitter such as an adrenergic

Acetylcholine is synthesized in the cytoplasm of nerve endings and is concentrated in their vesicles. Nerve stimulation causes a release of ACH from the presynapses. It rapidly becomes bound to specific receptor molecules in the postsynaptic membrane. This initiates permeability to small ions, e.g., Na+, which depolarize the postsynaptic cells. ACH tends to be excitatory at the presynaptic terminals and inhibitory at the postsynaptic membrane (52, 53). Ca++ and Na++ increase ACH release and Mg++ decreases it (53). Botulinum toxin prevents ACH release. ACH has an excitatory action on the medulla, hypothalamus, midbrain, thalamus, and cerebral cortex. In the midbrain, ACH in some cells exerts an excitatory action, in some inhibitory, and in some no response (50). Many of the cholinergic neurons of the CNS form a great ascending system of neurons originating from cell bodies in the reticular formation and radiating to all parts of the forebrain; there are radiations especially to the hypothalamus, thalamus, visual pathway, striatum, hippocampus and neocortex. This system presumably is responsible for electrocortical arousal involved in consciousness and the wakened state. Neither physostigmine nor atropine influences permanent memory, but learning and retention are significantly affected by them. Cholinergic drugs cause a defect in recent memory.

The levels of acetylcholine in intact nervous structures tend to be relatively constant during one state of physiological activity, because synthesis rapidly keeps pace with release and degradation keeps pace with increase in ACH synthesis. Synthesis results from actions in choline acetyltransferase. This enzyme is found in high concentrations in the brain, particularly the caudate nucleus and parts of the optic nervous system. It is found chiefly in nerve endings. The rate of synthesis depends upon the equilibration of choline acetyltransferase and substrates and products. An increase in Na+ intracellularly stimulates acetyltransferase and substrates and products. An increase in Na+ intracellularly stimulates acetyltransferase and substrates and products. ACH inhibits this enzyme. The synthesis of ACH is controlled somewhat by its accumulation in synaptic vesicles.

ACH is very rapidly hydrolyzed, particularly at the postsynaptic membrane, by acetylcholine esterase. The products are acetate and choline. The choline may be reused in ACH synthesis. The ACH tends to inhibit its own hydrolysis. The acetylcholine esterase is found in all innervated tissues, but is highest in the membrane of cholinergic post synapses.

Drugs that stimulate the central nervous system tend to increase ACH levels. Among the drugs that increase the levels are: carbamylcholine, physostigmine, eserine, pentobarbital, and tetramethylammonium ion. Among the drugs that decrease the level of ACH are: scopolamine, benactyzine and atropine. Central anticholinergic drugs may exhibit hallucinogenic effects (50). Thiamine is needed in the synthesis of ACH because acetyl CoA production from pyruvate depends upon it. Of course, neurologic symptoms occur when the thiamine content decreases below 25% (55). Some patients with lesions in the
vicinity of the hypothalamus have exhibited episodes of marked anger and rage. Release of NE by brain stem neurons is associated with rage reactions. The release tends to be maximal in medullary regions, which appear to be inhibitory to some or all of the autonomic and somatic components associated with this type of behavior (56).

Among a large number of prisoners with habitual aggressiveness, 57% had abnormal electroencephalograms, vs. 12% in ones who had committed a single violent crime. The site of abnormality was often found to be in the temporal lobe (57).

In rats that ordinarily do not kill mice, it has been shown (58) that lateral hypothalamic injection of carbamylcholine elicits killing (Fig. 5). NE, amphetamine, 5-HT and sodium salts injected at the same site were ineffective. Moreover, carbamylcholine was ineffective when injected into the medial, dorsal or ventral hypothalamus. A cholinesterase inhibitor, neostigmine, elicited killing, whereas a cholinergic blocker, methylatropine, inhibited killing. Thus, these experiments demonstrate the pronounced effects of alterations and levels of neurohuroners on behavior.

Catecholamines. The main catecholamines found in the brain are NE and DA. There is relatively little EPI. None of the three penetrates the blood brain barrier to a significant degree. However, precursors of them, namely, tyrosine and DOPA, penetrate well. The mechanism of synthesis of these catecholamines is like that in other parts of the body. Following manufacture, the catecholamines are stored in granules in the presynaptic nerve endings and are released into the synaptic cleft in response to nerve impulses (59). Tyrosine hydroxylase is distinctly the rate-limiting step in NE synthesis (60).

DOPA decarboxylase is relatively non-specific. It decarboxylates 5-HT, histidine, phenylalanine, tyrosine and other amino
acids (61). With nerve stimulation, release of NE is immediately associated with increased NE synthesis (60, 62). Tissue levels of NE tend to remain constant even with stress, unless NE synthesis is inhibited. It is bound in the vesicle in a complex with adenosine triphosphate, Mg++, and protein. Only the amines bound in vesicles are released by nerve stimulation. When the binding is prevented, e.g., by reserpine, even the NE in soluble form is not released (60). Phenylethanolamine N-methyltransferase catalyzes the conversion of NE to EPI. It is found chiefly in the adrenal medulla, although there is some in the brain. The release of NE is related more to the intensity than to the quality of stress. EPI is released when there is uncertainty, need for fight or immediate flight, or some other vigorous exercise (63). NE is released particularly in situations where there might be a great blood loss, with associated drop in blood pressure; it is also produced in situations where the outcome is inevitable or unavoidable—in those situations where muscle activity is not needed, e.g., operations.

NE mediates alertness, wakefulness, pleasure, euphoria, anger and fear (63). DA and 5-HT make some contributions in these situations. The amount and type of reactions to NE depend upon the setting and past experiences of the individual. When the organism is confronted with certain stressful situations encountered previously, there tends to be less EPI and relatively more NE (64). NE excites certain brain areas and inhibits others (65). NE and ACH increase the phosphorylation of phosphatidic acid and this is important in memory, learning and adaptation (65).

A neuron takes up a significant amount of NE that has been released from the cell and stores it in intraneuronal vesicles. High concentrations of NE are found in the base of the brain, especially the hypothalamus and medulla and pons (66). Following 3H-NE intravenously, very little is taken up by the brain, excepting the hypothalamus (67). Similar results follow the administration of EPI. DA is found predominantly in the caudate nucleus, substantia nigra, striatum and pallidum (66, 68); it has a high order of turnover. In extrapyramidal centers, it exerts inhibitory and excitatory activities (68). It is the main catecholamine in the median eminence and retina. There is a marked decrease in its level in the aforementioned areas in parkinsonism. Large doses of DOPA markedly increase DA without an increase in NE, but with a decrease in 5-HT (69). After injection of 3H-dopamine into the lateral ventricle, the largest amount was found in the striatum (70). Very little EPI is found in the brain and most of that is in the hypothalamus (67). There is much less of it also in the peripheral nerves than NE; it comes chiefly from the adrenal medulla (66). As mentioned earlier, there is an increase in the catecholamines in the brain with mania and a decrease with depression.

The catecholamines are degraded chiefly by MAO and COMT. MAO is found inside the neurons, chiefly in mitochondria (61). It inactivates the amines by oxidative deamination. However, it does not degrade the catecholamines that are stored in the vesicles (62). It inactivates very rapidly the nonvesicular, intracellular catecholamines and 5-HT. When reserpine releases NE, degradation is mainly via deamination (60).

Both in the nervous system and peripheral tissues, COMT activity is generally lower than that of MAO. Whereas COMT activity is exclusively related to catecholamine metabolism, MAO acts on certain other amines such as 5-HT. In the brain, the distribution of COMT correlates fairly well with that of endogenous catecholamines (61). Most of COMT in the body is found in the liver and kidneys (61, 62). It converts what is released from nerve endings to normetanephrine (59). When NE is metabolized after being released onto the receptor, it is O-methylated (60). A significant
amount of NE from the brain is excreted as 3-methoxy-4-hydroxy phenylglycol, but very little of NE from noncerebral sources is excreted in this form (71). This metabolite has been found low in the urine of depressed patients, while the normetanephrine and metanephrine levels were normal (71).

Many drugs are used for increasing or decreasing the levels of catecholamines, because these compounds influence so significantly the behavior. Tricyclic antidepressants increase catecholamine activity by decreasing NE uptake by the neuronal membrane, thereby avoiding exposure to degradation by MAO. They also inhibit the uptake of other amines (72). Harmaline and amphetamine are reversible competitive inhibitors of MAO; among the irreversible inhibitors are: iproniazid, phenelzine, isocarboxazide, malamide, and tranylcypromine (61). MAO inhibitors markedly increase the catecholamine content of neurons. Reserpine and related compounds apparently destroy the intraneuronal binding sites for catecholamines and this markedly decreases their intracellular level, since they are readily exposed to MAO. Extraneuronal deamination seems to occur only after primary methylation (61). There are relatively few inhibitors of COMT that are used clinically.

Reserpine, tetrabenazine, and other benzoquinolizines release equal amounts of NE and 5-HT. Depending on the balance between these two resides the induction of depression by benzoquinolizines. NE is reduced relatively more than 5-HT, because there is a much larger quantity of the latter initially; with low NE 5-HT sedation often results (73). 6-Hydroxydopamine decreases the brain catecholamine level without significant change in 5-HT. α-Methyl-5-HTP decreases tissue levels of catecholamines (68, 74). 5-HT can decrease brain NE more than 50% in two hours (75); this presumably results in inhibition in the synthesis of NE by amino acid decarboxylase. Imipramine and desmethyl-imipramine decrease the NE uptake by the axonal membrane (62), thereby increasing the catecholamine activity. Small doses of thyroid hormone given with imipramine cause increased catecholamine activity. In this manner there is a benefit to depression (76).

Alterations in catecholamine metabolism influence enormously normal behavior, and are very much involved in abnormal behavior, particularly in depression, mania, anxiety neurosis and possibly in schizophrenia.

Serotonin. Serotonin greatly influences behavior. It affects the emotional reactions and the level of intellectual performance (77). It depresses a number of activities, but over long intervals it facilitates the recruiting and synchronizing systems. When injected in cerebral ventricles, it markedly increases body temperature while catecholamines decrease it (78). These effects presumably are mediated by the hypothalamus. It is conjectured that 5-HT may exert a number of its effects by constriction of blood vessels (79). There are a number of studies that have suggested that an alteration in 5-HT metabolism exists in schizophrenia. With worsening of behavior in such patients, there is an increase in urinary tryptamine.

Serotonin is found in bound and free form, chiefly in the vesicles of nerve terminals. It is bound to a special proteolipid but not to gangliosides (80). The level in the cell bodies themselves is low. 5-HT is found chiefly in nerve terminals that contain other biogenic amines (80). Particularly high concentrations are found in the hypothalamus, pineal, raphé nuclei of the lower brain stem, and in terminals diffusely scattered in most of the reticular formation, with some in the surrounding pyramidal tracts and medioventral part of the caudal tegmentum. Virtually all of the brain contains some 5-HT (81) but there is very little in the diencephalon, telencephalon, and spinal cord. The largest number of
serotonergic nerve terminals of sympathetic and parasympathetic nuclei are in the lumbar enlargement and the sacral portion of the cord; it is also concentrated in some visceral efferent nuclei of the pons and medulla (78). Very little serotonin crosses the blood brain barrier, whereas its precursor, 5-HTP, readily crosses it. Serotonin is synthesized and degraded in the central nervous system. The hydroxylation of 5-HTP by tryptophan hydroxylase is the rate-limiting reaction. Both the hydroxylase and the decarboxylase tend to be located in the nerve endings (78). 5-HT is released by nerve stimulation or by K+. The ability of ouabain to suppress electrically conducted release suggests the need for transport of Na+ for the depolarization-induced release of it. It is degraded by MAO to 5-hydroxyindolacetic acid.

The level of 5-HT is increased by 5-HTP and by MAO inhibitors (77), e.g., iproniazid or malamide (78). Imipramine increases it by decreasing its reuptake and degradation by MAO. Chlorpromazine, desipramine, LSD, lithium, and ouabain markedly inhibit 5-HT release after electrical stimulation (82). Corticosterone increases it by way of increasing tryptophan hydroxylase activity (79). Reserpine lowers 5-HT via increasing the amount degraded by MAO. Chlorpromazine combines with 5-HT receptors and thereby blocks 5-HT action (77). Phenylalanine inhibits its synthesis: thus, 5-HT is decreased in PKU; this is somewhat prevented by the administration of melatonin or 5-HTP (77). p-Chlorophenylalanine, α-methyl-DOPA and catecholamines decrease 5-HT level by blocking tryptophan hydroxylase activity. Compounds with structures similar to 5-HT, e.g., medmain, benzylidimethylthamca, and LSD produce a schizophrenic-type picture (77, 78). Such compounds may produce a variety of personality changes, hallucinations, pleasant sensations, excitement, agitation and violence. Some of these compete with 5-HT for its receptor-binding site, whereas others exert an action like 5-HT.

An excess of 5-HT synergists has been reported in the tissues of schizophrenics, thought possibly to be a ganglioside (77).

LSD increases the 5-HT in brain and interferes with serotonergic nerve transmission (78); it acts on serotonin receptors. Another natural analog that produces a schizophrenic type of picture is psilocybin. With a decrease in serotonin levels in the brain, depression tends to occur, along with insomnia.

Histamine. There is significantly less histamine in the brain than 5-HT and catecholamine. Mast cells are not found in the central nervous system of man. The highest levels of histamine are in the hypothalamus, colliculi, thalamus, and especially median eminence, pituitary stalk and the pituitary (83, 84). It forms complexes with acidic lipids and other acidic substances, including sulfomucopolysaccharides which are present in the gray matter of the brain. There is less in the white matter. It is concentrated especially in the synaptic vesicles. The large amounts in which it is found in the postganglionic fibers suggest it might participate in the regulation of the sympathetic nervous activity. Very little histamine passes the blood brain barrier. It is formed by decarboxylation of histidine, which passes readily. It is degraded by methyltransferase to form methylated histamine. Its levels in the brain are very much influenced by psychotropic drugs. Chlorpromazine increases its level in the hypothalamus by as much as 50% and in the medial thalamus by 30%, this resulting from inhibition of histamine methyltransferase. Iproniazid increases histamine in the hypothalamus (83). Not much is known about the mechanism and extent to which it influences behavior; it is a weak depressant.

Other neurotransmitters. The role of other neurotransmitters seems less well established. This group includes GABA, glutamate, aspartate, glycine, and prostaglan-
GABA is derived chiefly from glutamate as a result of the action of glutamate decarboxylase. Upon reacting with the postsynaptic receptor, it causes this membrane to become more permeable to chloride. It has a unique occurrence in the mammalian nervous system. The highest levels are in the outer layers of the cerebral cortex. GABA depolarizes cortical neurons, exerting an inhibitory action. Stimulation of inhibitory axons leads to release of GABA, whereas stimulation of excitatory nerves does not degrade GABA. It is degraded by GABA glutamate transaminase. It produces a hyperpolarizing potential change similar to a naturally elicited inhibitory potential (88). It is suggested that the total output of the cerebellum is inhibitory. Glutamate is the most abundant of the amino acids in the brain. Indeed, the concentration is higher there than in any other tissue. The level is higher in the cerebral hemisphere and in the cerebellum than in the midbrain, pons and medulla, but it has a ubiquitous distribution. Its amount decreases during sleep (86). It exerts an excitatory action by promoting depolarization of the cell to a level of membrane potential near zero. It is found in about equal amounts in the excitatory and inhibitory neurons (87). Aspartic acid is an excitant, acting chiefly in the spinal cord. Glycine is found in moderate amounts in nervous tissue; its concentration in the pons and medulla is twice that of the midbrain and three times that in the cerebral hemispheres and cerebellum. It has a depressant reaction on cortical neurons but less than that of GABA (86). It has more action on the spinal cord than in the brain.

At all transmission sites in the CNS, there is an inhibitory antagonism to the generation of impulse discharge by the excitatory synapses. There are specialized neurons with no function other than inhibition. These send off recurrent collateral endings in the excitatory synapses. When a nerve discharges an impulse, it automatically activates inhibitory impulses (90). Glucose is a potent source for brain glutamate, glutamine, aspartate and GABA. Of course, glucose exerts many other important functions in the brain (91).

Of the many amino acids found free in the aqueous phase of the brain, glutamate and aspartate together with their close chemical derivatives account for about 80%. Taurine and cystathione are among the more prominent of the amino acids. Ammonia is liberated during nervous activity. Its concentration in the brain increases sharply during convulsions and decreases during sleep.

As discussed earlier, hyperphenylalaninemia is found with PKU and associated with impairment of mentation. However, that such does not always occur is indicated by the observation (92) of two adult brothers with this disorder in an untreated state. Each had hyperphenylalaninemia. One had a mental deficiency, whereas the other one had hypernormal intelligence. The former had a decrease in plasma glutamine. Among 12 other mentally defective untreated PKU's, there was hypoglutaminemia (92), whereas a group of PKU children on low phenylalanine diets did euglutaminemia. Prostaglandin E1 and E2 suppress the NE effect on the cerebellum.

Adenosine 3',5'-cyclic monophosphate. The brain has the highest level in the body of adenosine 3',5'-phosphate and of the enzyme responsible for its synthesis, adenylic cyclase, and the one responsible for its degradation, phosphodiesterase (93, 94). Significant increases in c-AMP are produced by NE, histamine, electrical stimulation and 5-HT (95, 96). These high levels of activity must be of great significance, but relatively little information is thus far available with regard to the functions accomplished by such. The rate of oxidation by glutamate is significantly increased by the c-AMP (97). C-AMP decreases the discharge frequency of Purkinje cells in rat cerebellum, whereas other nucleotides tested
accelerate the discharge rate of most units (98). The urines of patients with mental depression have subnormal levels of c-AMP, whereas urines of manic patients have distinctly hypernormal levels. Tricyclic antidepressants inhibit c-AMP degradation, and it is possible that this is an important mechanism for the relief of the depression (99).

References

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