Chapter 32

Nutrition in Schizophrenia and Major Depressive Illness: A Review of the Research

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INTRODUCTION

Eating disorders are categorized in DSM III as five distinct clinical entities: anorexia nervosa, bulimia, pica, rumination disorder of infancy, and atypical eating disorder [1]. Peculiar eating patterns have been observed in patients with schizophrenia and affective disorders; however, such eating disturbances are not considered primary determinants of the active phase of the illness [2]. Instead, the eating disturbances seen in schizophrenia are viewed as secondary manifestations of hallucinations or psychotic delusions, e.g., an acutely uncompensated patient who is paranoid and delusional about his food being poisoned may seriously restrict his caloric intake [3]. After recompensation with the return of improved reality testing, the schizophrenic patient may increase his caloric intake to more stable levels. Depressive episodes have been associated with appetite disturbances resulting in predominantly decreased appetite and weight loss. Less frequently, depressed patients may experience increased appetite with carbohydrate craving leading to a weight gain [4-6]. Like the schizophrenic eating disorders mentioned above, these appetite disturbances are also seen as state dependent; the appetite will return to normal as the depressive illness is resolved. Therefore, the appetite disturbance is seen as a secondary manifestation of the active phase of the illness and not causally related to the onset of the depression.

A question arises concerning appetite disturbance or altered dietary patterns seen in major psychiatric illness. Is it really a secondary manifestation of the disease in all instances, or is it primary to the disease process itself in some instances? Leckman et al. [7], using a post hoc analysis of 810 first-degree relatives of 133 depressed and 82 normal probands, found that relatives of depressed individuals who reported symptoms of appetite disturbance and excessive guilt were at 2.5 times greater risk for a major depressive episode than relatives of depressed individuals lacking either or both of these symptoms. Furthermore, Leckman et al state, "The finding that appetite disturbance is a powerful predictor of risk in first-degree relatives suggests that the neurochemical and neurophysiological mechanisms that regulate appetite may be closely linked to some forms of depressions." [7]

Additional support for the relationship between appetite regulation, food consumption, and psychiatric illness comes from the animal studies of Wurtman and his associates on dietary precursor control of brain neurotransmitter metabolism [8-12]. The brain synthesis of the neurotransmitter serotonin has been shown to be influenced by the plasma availability of its dietary precursor tryptophan; the plasma availability of tryptophan has been shown to be influenced by the ratio of carbohydrate to protein consumed in the diet. Conversely, serotonergic mechanisms have been implicated in the con-
control of food choice: specifically, the ratio of carbohydrate to protein consumed during each meal. Serotonin has also been associated with depressive illnesses and less frequently with schizophrenia. There are other neurotransmitters that are also influenced by dietary precursors: acetylcholine, the catecholamines (dopamine and norepinephrine), histamine, and glycine [8,9]. Abnormalities in dopamine metabolism have been linked to schizophrenia [13,14], norepinephrine to depression and mania [15,16], and acetylcholine to affective illnesses, tardive dyskinesia, and several neurological diseases [8,9].

Wurtman and his group have also demonstrated that brain neurotransmitter synthesis in animals can be altered by dietary manipulations. The administration of megadoses of normal dietary constituents such as tryptophan and tyrosine with carbohydrates have resulted in increased levels of CNS serotonin and catecholamines. These two findings, that dietary precursors exert control over brain neurometabolism, and that dietary manipulations can effectively alter brain neurotransmetabolism refute (with the exception of glucose) the previously held theory of the independence of brain function from dietary intake. The new theory documented by Wurtman and his associates proposes that brain neurometabolism is dependent on the plasma availability of ingested nutrients [8,9,17].

Abnormalities in the synthesis of brain monoamines (serotonin, dopamine, and norepinephrine) have been implicated in psychiatric illness: dopamine in schizophrenia and serotonin and norepinephrine in affective illness. As Wurtman and others have shown, measurable changes in brain monoamine synthesis may be influenced by the plasma availability of tryptophan and tyrosine, the substrates for monoamine synthesis.

Other nutrients that are required for the synthesis of brain monoamines are the amino acid methionine, the vitamins pyridoxine and ascorbic acid, the metals iron and copper, and oxygen [18]. The nutrients methionine, folic acid, and vitamin B₁₂ interrelated with s-adenosylmethionine (SAM) in transmethylation reactions have been implicated in influencing monoamine synthesis [19]. These nutrients have also been associated with psychotic and affective disorders [20-23].

A large body of research on the biochemistry of schizophrenia has evolved from the "dopamine hypothesis". The "biogenic amine hypothesis" has also stimulated much research on the biochemistry of major affective illness. Nutrients that are involved in the metabolism of the brain monoamines may influence brain monoamine synthesis and thereby play an important role in the biochemical substrate of schizophrenia and major affective illness [8,9,18,24].

The fact that brain function can be affected by ingested nutrients gives importance to an investigation of nutrition and brain function. Currently, dietary and nutritional factors have been given little significance in major psychiatric illness. The literature is devoid of any body of research concerning dietary intake and pattern in humans, and its relationship to mental illness outside of work done on the medical complications of anorexia nervosa and bulimia. The typical clinical, medical, and psychiatric history usually does not include dietary history. Furthermore, accurate clinical assessment of dietary intake of nutrients by history is problematic. Much of the research has focused on correlative studies of serum vitamin coenzyme deficiencies in psychiatric populations: the data have been interesting but inconclusive [24]. The claims of successful treatment of schizophrenia by orthomolecular psychiatrists, through their use of megavitamin therapy, have met with much skepticism because of the absence of double-blind clinical investigations [25].

This chapter will synthesize the literature on the role of some of the more thoroughly investigated nutrients in the biochemistry of schizophrenia and major depression. Other associated biochemical factors, including disturbances of water metabolism and wheat gluten enteropathy, will also be reviewed.

Only schizophrenia and major depression will be considered. These two illnesses seem to have strong genetic loading with biochemical abnormalities that are the most thoroughly investigated to date. Alcoholism and its effects on brain functions has been extensively studied elsewhere [26] and will not be covered in this chapter.

**SECTION I: SCHIZOPHRENIA**

**WEIGHT CHANGES AND DISTURBANCES OF WATER METABOLISM IN SCHIZOPHRENIA**

Weight Changes

Schizophrenia has been associated with eating disturbances, weight fluctuations, and disturbances of water metabolism. In the era preceding the introduction of phenothiazines in 1954, there were numerous reports concerning the organic findings present in schizophrenia [27-31]. Bleuler [28] described the course of dementia praecox (schizophrenia) as characterized by weight fluctuations from "extreme marasmus to excessive obesity and the reverse. In acute disease the bodily weight usually diminishes, and increases during convalescence." Mayer-Gross and Walker [32] stated, "schizophrenics sometimes refuse food, others devour...
everything they can get hold of regardless of taste." Freeman [33] describes acute psychosis as being preceded by a weight loss and clinical improvement by a weight gain. Freeman associated the psychiatric symptoms and weight changes as being caused by some "central mechanism."

Crammer [34] investigated the relationship between mental changes and rapid weight fluctuations in three medication-free patients with periodic catatonia, a rare form of schizophrenia. Clinically, these patients cycle through acute stuporous or excited catatonia at approximately regular intervals, and then recompensate between periods to near "normal behavior." For example, one case reported was of a 38-year-old man hospitalized for five years with periods of decompensation lasting ten days, characterized by unpredictable, excited, hostile behavior and stereotypic speech, followed by periods of recompensation and stability occurring at 23- to 30-day intervals.

The study data revealed cyclical weight fluctuations that corresponded to the course of the psychosis: rapid weight loss within a 24-hour period (maximum 9 lb per 24 hours) preceded the development of acute psychosis, the regaining of the lost weight was associated with clinical improvement. Crammer considered the weight loss as a physical sign of the pathological process of the illness and he explained the pathophysiology of the rapid weight loss as probably related to fluid and electrolyte imbalance. He recommended further study on the regulatory glands controlling fluid and electrolyte balance.

Holden and Holden [35] investigated weight changes in 22 chronic schizophrenic males taking psychotropic medications and placebo at eight-week intervals, employing a double-blind crossover design. Behavior assessment was done by rating scales including the BPRS. The data for the placebo period revealed a significant correlation between weight fluctuations and psychosis: weight loss preceded worsening of psychosis and weight gain predicted clinical improvement. There was also some significant correlation between weight change and psychosis during some of the drug periods. The authors suggested that changes in weight may be primary to the psychotic disease process. In addition, hypothalamic-pituitary function may be involved in this process.

In summary, central mechanisms [33], hormonal regulation of fluid and electrolytes [34], and the hypothalamic-pituitary axis [35] all have been implicated in the weight change observed in schizophrenia.

Fluid and Electrolyte Balance

Fluid and electrolyte disturbances have been reported in schizophrenia. Hoskins and Sleeper [31] reported on the 24-hour urine volume of 92 male schizophrenic patients. The authors found a larger (2602 ml versus 1328 ml) average daily urine volume in the schizophrenic patients compared with the male control subjects. A recent report by Lawson et al [36] found similar results while comparing the 24-hour urine volumes of 35 medication-free chronic schizophrenic patients, 31 control subjects, and 7 medication-free nonschizophrenic patients with various diagnoses. The schizophrenic patients' mean urine volumes were significantly higher than the other two groups (2319 ml versus 1054 ml).

Polyuria has been associated with psychogenic polydipsia (compulsive water drinking) in the schizophrenic population [37-41]. Smith and Clark [40] reported on 21 schizophrenic patients developing water intoxication secondary to polydipsia. The authors also cited 25 other cases in the literature of water intoxication with the majority of these cases having a diagnosis of schizophrenia. Water intoxication causes severe dilution of the body fluids resulting in hyponatremia. Early symptoms include nausea, vomiting, headaches, increased perspiration, difficulties in coordination, and excitability. Late symptoms are tetany, delirium, seizures, and coma [41].

Dopaminergic neurons implicated in the biochemistry of schizophrenia may also be implicated in the abnormalities of body weight and water metabolism. The hypothalamus regulates thirst as well as appetite [42]. Dopaminergic neurons have been located in the hypothalamus [43]. Dopaminergic neurons have been shown to influence thirst in rats: Dopaminergic agonists increase water intake in rats while the dopaminergic antagonists decrease water intake in rats [44]. Dopaminergic neurons have also been shown to influence feeding in rats: Dopaminergic agonists decrease feeding in rats while dopaminergic antagonists increase feeding [43,45,46]. Psychotropic drugs shown to alter brain dopaminergic activity may also affect appetite in humans [47,48].

Some cases of polydipsia and secondary polyuria have been associated with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion [40]. Dopamine has also been implicated in neural antidiuretic hormone regulation [40,49].

COOLES and Borthwick [50] reported a case of SIADH in association with Wernicke's encephalopathy that showed an improved clinical response of both Wernicke's encephalopathy and SIADH to intravenous therapy with vitamin B complex. Kremen and Kremen [51] reported a case of SIADH in association with hypomagnesemia that was responsive to magnesium repletion. The role of these agents in the abnormalities of water metabolism in these two cases is interesting. Some cases of anorexia nervosa have also been linked to ADH abnormalities [52].
Rapid weight changes have been observed in schizophrenic patients in the preneuroleptic era. As Crammer [34] suggested in 1957, such rapid weight losses were probably due “to losses of body water and its associated salt; ...the loss was probably urinary.” Schizophrenic medication-free patients have also been reported to have disorders of water metabolism manifested by polydipsia and polyuria. The underlying mechanism may involve neural-hormonal regulation of thirst and water metabolism mediated by dopamine. Weight fluctuations in schizophrenic patients may also involve neural-hormonal mechanisms affecting appetite regulation mediated by dopamine. The interrelationship between abnormalities in dopamine and appetite and water metabolism in schizophrenia warrants further scientific delineation.

OTHER BIOCHEMICAL THEORIES OF SCHIZOPHRENIA

The principal biological hypotheses for the pathogenesis of schizophrenia implicate neurotransmitters, neurotransmitter imbalances, neurotransmitter binding site densities, and toxic metabolites forming endogenous hallucinogens [53-55] (the psychological theories will not be covered here).

The dopamine hypothesis of schizophrenia postulates an increased dopaminergic activity in the brains of schizophrenic patients [13,14,53]. The presumptive defect occurs at the nerve synapse either presynaptically or postsynaptically at dopamine receptors. Evidence supporting the dopamine hypothesis comes from pharmacological studies [53]. Neuroleptic agents that alleviate schizophrenic psychotic symptoms also reduce brain dopaminergic activity. This has been demonstrated in human and animal studies [13,14,52]. In addition, the more potent the antipsychotic agent, the greater the dopamine receptor blockade [56-57]. Conversely, agents that increase cerebral dopaminergic activity (such as amphetamine or cocaine) can cause psychosis indistinguishable from acute paranoid schizophrenia [58].

A major flaw in the dopamine hypothesis, however, is a lack of substantial direct evidence of altered dopamine concentrations or their metabolites in the central nervous system of schizophrenic patients [53]. It has been reported that amphetamines, L-dopa, apomorphine, and monoamine oxidase inhibitors, substances that should, according to the dopamine hypothesis, always aggravate schizophrenic symptoms, have in some cases resulted in clinical improvement [55].

As a consequence of these inconsistencies in the dopamine hypothesis in satisfactorily describing the etiology of schizophrenia, other neurotransmitters have been investigated and implicated. These other neurotransmitters are norepinephrine, gamma-aminobutyric acid (GABA), and acetylcholine. Norepinephrine is a product of the hydroxylation of dopamine by an enzyme, dopamine beta-hydroxylase. GABA is an inhibitory neurotransmitter that is believed to affect dopaminergic activity.

Acetylcholine is a neurotransmitter postulated to be in dynamic balance with dopamine in the brain [53,55]. Enzymes significant in the metabolism of these neurotransmitters such as dopamine beta-hydroxylase (DBH) and monoamine oxidase (MAO) have also been investigated. DBH, as already mentioned, is an important enzyme in the conversion of dopamine to norepinephrine. MAO is an important enzyme in the metabolism of both dopamine and norepinephrine.

Investigations of these neurotransmitters and enzymes have resulted in suggestive but inconclusive evidence [53,55] of their role in schizophrenia. What is apparent, however, is the complexity of the interrelationship of these few neurotransmitters and enzymes and how an imbalance in any one component may affect the whole system because of their dynamic interactions. Cooper et al [59] describe the direction of future research on neurotransmitters in the introduction of their book The Biochemical Basis of Neuropharmacology, “...to explain the function of integration of the approximately three dozen classical neurotransmitters, neuroactive peptides and the unclassifiable items, such as adenosine, in eliciting behavioral changes.” The few neurotransmitters investigated thus far may only delineate a small portion of the complex interrelationship. However, it is a necessary step toward increasing the understanding of the biochemistry of schizophrenia.

The formation of endogenous hallucinogens by toxic metabolites is another hypothesis long under investigation as a possible factor in the pathogenesis of schizophrenia. Naturally occurring hallucinogens, such as LSD or mescaline, are known to produce symptoms of psychosis in otherwise normal individuals. The putative formation of endogenous hallucinogens by some inborn defect in neurotransmitter metabolism was first investigated in 1952 by Osmond and Smythies [60]. They were impressed with the similarity of structure between mescaline and epinephrine. Hoffer et al [61] suggested that adrenochrome, an oxidation product of epinephrine, was the highly toxic, mescaline-like metabolite present in schizophrenia. It supposedly resulted from an abnormal methylation of epinephrine in schizophrenic patients. The abnormal methylation process, according to the investigators, could be inhibited by a strong methyl acceptor, such as niacin or nicotinic acid [62].
Niacin was employed in megadoses of greater than 3 grams daily (RDA 18 mg per day) [63]. In 1957, Hoffer et al [62] tested the clinical efficacy of niacin in reversing schizophrenic symptoms. Dramatic claims of success were made, but other researchers employing double-blind measurements could not replicate the original claims of success [24,64].

In the 1960s and 1970s the “methylation hypothesis” evolved from the sole use of nicotinic acid as a therapeutic agent to a variety of vitamins and nutrients. These included nicotinamide adenine dinucleotide (NAD), a coenzyme derived from vitamin B3 to megadoses of multiple vitamins: vitamin C, B6, folic acid, B12, pantothenic acid, other vitamins, hormones, minerals, diets, etc [29,64].

The megavitamin therapies were given added support by Pauling in 1968 [65]. Pauling subsequently defined orthomolecular psychiatry as “the achievement of preservation of mental health by varying the concentrations in the human body of substances that are normally present, such as the vitamins” [66]. Schizophrenia, theorized Pauling, was caused by an abnormal enzyme that leads to a defective coenzyme-apoenzyme system. This results in the formation of an inactive enzyme, leading to a cerebralavitaminosis. Pauling stated that the decreased affinity of the apoenzyme to the defective coenzyme can be overcome by increasing the amount of coenzyme (vitamin): this would lead to an active holoenzyme. Pauling’s hypothesis that schizophrenia is a vitamin-dependency illness provided a rational basis for the use of megavitamin therapy. Principles of orthomolecular psychiatry have been viewed as plausible and reasonable, but without sufficient scientific evidence to support this hypothesis or treatment modality [64,67]. Furthermore, the orthomolecular group has been cited for failure to use adequate research methodology, including lack of double-blind studies, nonrandom use of subject and experimental design, inaccuracy of measuring instruments, and lack of a testable hypothesis [24].

Megavitamin therapy or orthomolecular psychiatry has been very controversial but it should be noted that Osmond and Smythies, in 1952, put forth the first modern biochemical hypothesis of the etiology of schizophrenia [68]. The current transmethylation hypothesis, according to Shulman, states that “Abnormal methylation of the neurotransmitted biogenic amines might result in the formation of endogenous hallucinogens” [69].

Some other examples of proposed endogenous hallucinogens formed by abnormal methylation are 3,4-dimethoxyphenylethylamine (DMPEA) and kryptopyrrole. DMPEA was initially found in the urine of schizophrenics but not normal controls. It was detected by chromatography, which revealed a “pink spot” [70]. Similarly, kryptopyrrole was found in the urine of schizophrenics; it was also detected by chromatography, which revealed a mauve-colored spot. The phenomenon was referred to as malaria [71]. The pink-spot hypothesis of schizophrenia and malaria were believed to be invalid because of the absence of these chemicals in many schizophrenics and their presence in normals [54,55].

Phenylethylamine (PEA), structurally and functionally similar to amphetamine, is another possible endogenous hallucinogen. It is formed by the decarboxylation of the amino acid phenylalanine. (Phenylalanine is also hydroxylated to tyrosine, which is a catecholamine precursor.) Potkin et al [72] found higher urinary concentrations of PEA in paranoid-schizophrenics than in other nonparanoid types of schizophrenic patients. Further investigation on PEA and its relation to schizophrenia is currently underway.

It is interesting that the work on PEA distinguishes a subgroup of schizophrenic patients, the paranoid-type, from the other subgroups of schizophrenics as to possible difference in pathogenesis. This is consistent with Bleuler’s [27,28] original view of schizophrenia in 1911 as having multiple etiologies, as well as current studies in clinical phenomenology, genetics, and biochemistry, which support the concept of schizophrenia being a complex disorder with multiple etiologies [53].

**NUTRITIONAL AND DIETARY FACTORS IN SCHIZOPHRENIA**

Folic acid is a vitamin that is part of the vitamin “B-complex” group. A deficient state in humans has been associated with a variety of psychiatric disturbances, including depression, organic mental states, psychosis, delirium, dementia, mental retardation, and sleep disturbance [24,73]. Freeman et al [74] reported an interesting syndrome in a 15-year-old girl with homocystinuria who developed schizophrenic-like behavior that responded to folate supplementation. Homocystinuria is an autosomal recessive disorder of amino acid metabolism. The disease is commonly caused by a deficiency of cystathionine synthase; several hundred cases have been reported. In the case of the patient with schizophrenic-like symptoms reported by Freeman et al, the biochemical defect was a deficiency in a folate-containing enzyme, 5,10- methylene-tetra-hydro-folate-reductase (methylene THF reductase). This enzyme is needed for the remethylation of homocysteine to methionine. The deficiency of methylene THF reductase results in the accumulation of homocysteine, which may be converted to homocystic acid, a potentially excitotoxic substance on the nervous system [75]. Megadoses of folic acid (eg, 20 mg/day, RDA [63] 400 mcg/day) appear to alleviate this type of homocystinuria.
According to the current literature there have been only four cases of methylene THF reductase deficiency resulting in homocystinuria. The clinical manifestations result in neurological symptoms including mental retardation, seizure disorder, electroencephalographic abnormalities, and musculoskeletal abnormalities [74-76]. One of these cases, as reported by Freeman [74], was a 15-year-old girl who exhibited a thought disorder with hallucinations, delusions, and catatonic posturing. When given folate supplementation psychiatric symptomatology disappeared. Upon the discontinuation of folate the psychotic symptoms would return. However, the patient had a sister who also had methylene THF reductase deficient homocystinuria who did not exhibit psychotic symptoms. Further investigation revealed that the psychotic sister had low platelet levels of monoamine oxidase while the nonpsychotic sister had normal MAO levels. Low levels of monoamine oxidase have been reported in schizophrenic patients [53,54], suggesting that the patient with psychotic symptomatology may have had increased vulnerability to schizophrenia. Furthermore, the abnormality of folate metabolism, leading to schizophrenic-like symptoms, may be hypothesized as representing only a part of polygenetic predisposition to schizophrenia [74].

The precise role of folate in improving the psychotic symptoms is unclear. The excessive accumulation of homocysteine resulting in homocystinemia is the unlikely causative agent, because homocystinemia patients with cystathionine synthase deficiency are rarely psychotic; several hundred cases have been reported with only a few cases with psychotic symptoms [75]. Reynolds [77] has stressed the organic factors present in the psychotic sister, which included a diffusely slow EEG that is more consistent with a metabolic encephalopathy, an organic psychosis rather than functional psychosis. However, the development of schizophrenic-like symptoms in a 15-year-old girl with an abnormality of folate metabolism responsive to folate supplementation is an interesting finding, especially since schizophrenia may be an illness with multiple etiologies.

Carney and Sheffield [78,79] surveyed 432 psychiatric patients for serum folate and vitamin B₁₂ levels. Twenty-three percent or 105 patients had low folate levels. Of these 105 patients, 20% were diagnosed as schizophrenics, 24% organic psychotics, 30% depressive, and 86% epileptics. A retrospective examination of the results of treatment with folic acid and vitamin B₁₂ was undertaken [79]. Among the low-folate groups, 39 were given folic acid and 63 were not. The folate-treated patients with schizophrenia, endogenous depression, and organic psychosis showed significant clinical improvement on discharge. However, external factors were present that may have resulted in the lowered folate levels: 14% also had decreased B₁₂ levels, 75% were taking various drugs for three weeks prior to the survey, 23% were malnourished, 17% were physically ill, and 44% chronically ill for more than three years. Furthermore, 86% of the low-folate group were diagnosed as epileptic and were probably on anticonvulsants, which are folate-depleting [24,80].

Carney did another survey on 272 newly admitted patients in 1972-1973. He found the proportion of patients with low folate levels to be 21%, similar to the previous study, and to be highly represented by depressives and organic psychotics. Similar to the previous study, preadmission drugs, malnutrition, and physical illness were more frequent among the low-folate group than among the normal-folate group. As Carney states, "Whether the observed folate deficiency is an effect or cause of the mental symptoms has not been established beyond doubt, but evidence has been advanced to support the hypothesis that in some patients folate deficiency can produce mental symptoms" [79].

Thornton and Thornton [73] reviewed the serum folate values of 269 psychiatric hospital admissions controlling for dietary habits, medications, and gastrointestinal illness. The psychiatric patients, compared with the 40 control subjects, demonstrated a greater incidence of low serum folate that could not be explained by poor diet alone. The authors concluded that other explanations should be investigated.

Cyanocobalamin, vitamin B₁₂, acts as a coenzyme in several reactions including the methylation of homocysteine to methionine (folate and B₁₂ cofactors), oxidation-reduction reactions, isomerization reactions, and methylation of soluble RNA [24,81]. Psychiatric symptoms reported with B₁₂ deficiency include dementia, confusional states, depression, and psychosis with hallucinations, delusions, and paranoia [24,82].

Zucker et al. [83] reviewed the literature and found 15 cases including one of their own that met specific criteria for B₁₂ responsive psychosis. Ten of the patients reviewed had paranoid delusions, seven had hallucinations, seven were depressed, and six had some degree of organic impairment. The authors reviewed the hematologic and neurologic findings, which were variable. Neurological and psychiatric symptoms were present in some cases in the absence of anemia. Psychiatric symptoms were variable; the most common in this review were paranoia, violence, depression, and organic brain syndrome. The authors asserted that symptoms of psychotic depression with organic mental impairment were factors that should increase the level of suspicion for a B₁₂ deficiency. Other important historical and physical findings present may include subacute combined
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Rimland [87], in a nonblind study of 191 autistic children, identified a subgroup of 20 autistic children who responded favorably to megadoses of vitamin B₆ and apparently relapsed upon withdrawal of B₆. In a follow-up study [88] on 16 of these autistic children who were positive responders to B₆ supplementation, vitamin B₆ and placebo trials were double-blinded to determine if significant deterioration of behavioral gains would occur upon withdrawal of pyridoxine in these patients. Behavior was determined by an individualized target symptom checklist rated by teacher and parent. Analysis of the data revealed a significant deterioration of behavior upon withdrawal of pyridoxine. Lelord et al [89] investigated the effects of B₆ therapy on the urinary homovanillic acid (HVA) levels of 33 autistic children. HVA is the principal metabolite of dopamine. The data revealed a decrease in the urinary HVA of the autistic children compared with an increase in the urinary HVA of the normal children acting as controls. Behavioral gains were reported in 15 of the autistic children. The reduction of the urinary HVA in the autistic children treated with pyridoxine indicates an abnormality of dopamine neurotransmetabolism in autistic children. As previously discussed, disorders of dopamine metabolism are implicated in schizophrenia [12,13].

Abnormalities in averaged evoked potentials have been reported in autistic children [90,91]. A study by Martineau et al [92] on 12 autistic and 11 normal children administered B₆ therapy revealed a tendency in the autistic group toward clinical improvement accompanied by the normalization of both the averaged evoked potentials and urinary homovanillic acid levels. (Magnesium was added to the B₆ regime to decrease reported incidences of irritability and enuresis associated with high doses of pyridoxine.)

Other neurotransmitter abnormalities, including serotonin and norepinephrine, have been reported in autism [93-95]. Interrelated neurotransmetabolism pathways may be involved. Pyridoxine’s involvement as a coenzyme in reactions affecting the serotoninergic, catecholaminergic, and GABAergic systems may play an important role in the etiology of childhood autism for a subgroup of genetically susceptible children. Further investigation appears to be indicated.

Niacin (nicotinic acid, vitamin B₃) in its active coenzyme form, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) is involved, as Lipton et al [24] state, “in glycolysis, the tricarboxylic acid cycle, electron transport reactions of mitochondria, and the hexose monophosphate shunt (pentose phosphate pathway).” NADPH, formed by a reaction involving malic enzyme, is utilized in fatty acid synthesis, steroid hydroxylases, phenylalanine hydroxylases and glutathione reduc-
tase." Tryptophan is a dietary precursor of niacin as well as a precursor of the neurotransmitter serotonin. Dietary tryptophan is converted to niacin in limited amounts in the liver via the kynurenine pathway, but probably not in the brain [24].

Niacin, when deficient, results in a condition known as pellagra, usually characterized by the "three Ds"—dermatitis, diarrhea, and dementia [63]. Psychiatric symptoms are diffuse and depend on the degree of deficiency. Mild deficiencies may present with apathy, depression, emotional lability, hyperirritability, anxiety, and memory deficits. Severe and chronic niacin deficiency may present as mania and delirium [24].

It was previously mentioned that in 1952 Osmond and Smythies [60] put forth the first modern biochemical hypothesis of the etiology of schizophrenia, the methylation hypothesis. This hypothesis proposed that schizophrenia was caused by an endogenous hallucinogen, adrenochrome, the result of abnormal methylation of epinephrine. Niacin was postulated to be a strong methyl acceptor that could inhibit the formation of adrenochrome from epinephrine. Early trials were promising with dramatic claims of success made for niacin. However, as previously stated, the original claims of success were never replicated and scientific evidence is currently lacking for niacin deficiency as an etiologic factor in schizophrenia or for the efficacy of niacin in the treatment of schizophrenia.

WHEAT GLUTEN ENTEROPATHY AND SCHIZOPHRENIA

Gluten, the protein part of certain grains including wheat, barley, rye, and oats, has been implicated in the etiology of schizophrenia by some investigators [96,97]. Gluten is the known pathogenic agent in celiac sprue. According to Trier [98], "Celiac sprue is a disease in which there is (1) actual or potential intestinal malabsorption of virtually all nutrients, (2) a characteristic though not specific lesion of the small intestinal mucosa, and (3) prompt clinical improvement following withdrawal of certain gluten-containing cereal grains from the diet."

In 1969, Dohan et al [96] investigated the effects of eliminating gluten from the diets of acute schizophrenics. One hundred and two acute schizophrenic patients admitted to a locked psychiatric unit were randomly assigned to two dietary groups. The control group was on a high-cereal (high-gluten) diet and the experimental group on a diet free of cereal and milk (gluten-free). Milk was omitted from the gluten-free group because some celiac patients experience exacerbation of symptoms after ingesting milk and dairy products, probably secondary to an associated lactase deficiency [98]. All patients received the usual prescribed treatment for this disorder including antipsychotics. Clinical improvement was assessed by how rapidly (measured in days) it took for a patient to be transferred to an open unit. In this study, transfer to an open unit occurred significantly faster in the gluten-free group. In the second part of the study, patients and staff were blind to the addition of gluten to the cereal-free group. The data indicated no significant difference in time of transfer to the open unit between cereal-free plus gluten and high-cereal groups. The authors concluded that the clinical improvement seen in the gluten-free group was not due to a placebo effect. In a follow-up double-blind study, Dohan and Grassberger [99] investigated 115 male schizophrenic patients admitted to a locked ward at a Veteran's Administration Hospital. The experimental group given a diet free of milk and cereal grains was discharged about two times faster than the control group on a high-cereal diet.

Singh and Kay [97], employing a double-blind crossover design, investigated 14 schizophrenic patients treated with neuroleptics on a locked research ward for the clinical effect of wheat gluten on the schizophrenic symptoms. Three types of independent rating assessments were obtained: a psychopathology rating schedule, social participation and avoidance behavior scales, and psychiatric interviews. The data indicated that schizophrenic patients on a cereal grain-free and milk-free diet showed clinical improvement but when wheat gluten was added to their diet, an exacerbation of the schizophrenia occurred. The authors concluded that gluten may be a pathogenic factor in schizophrenia.

Rice et al [100] investigated the clinical response of 16 chronic schizophrenic patients treated with neuroleptics to the addition and elimination of wheat gluten from their diets. Two of the patients showed clinical improvement as measured by the Brief Psychiatric Rating Scales (BPRS) on a gluten-free and milk-free diet. One of these two patients, a 29-year-old chronic paranoid schizophrenic hospitalized for 15 years, decompensated during the gluten challenge phase of the study. The patient became severely agitated, uncooperative, and paranoid. The other patient, hospitalized for 13 years, showed such significant improvement that she was discharged to her family. Potkin et al [101] in a double-blind study of eight chronic schizophrenic patients, found no evidence of clinical deterioration or improvement on the BPRS to gluten challenge or withdrawal.

In 1966 Dohan [102,103] did an epidemiologic investigation of schizophrenic admissions during World War II because, in various parts of the world, cereal grains were scarce and the consumption of wheat was greatly
was abundant, schizophrenic admissions were increased. DoGAN et al. [104] investigated tribal populations of the South Pacific Islands, where cereal grains were scarce, for the incidence of schizophrenia. Public Health Medical Officers and anthropologists observed only two florid schizophrenics in more than 65,000 adults examined in Papua, New Guinea (1950-1967), Malaita, Solomon Islands (1980-1981), and Yap, Micronesia (1947-1948). The prevalence rate expected by the author would have been 2/1,000 adults or 130.

These figures are based on the prevalence of schizophrenia in Europe prior to the neuroleptic era. Hallert and Astrom [111,112] proposed that there is a strong correlation between celiac disease and depressive illness. They investigated an area of Sweden where the prevalence rate for celiac disease was high at 1/1,000. The authors, in a retrospective examination of celiac patients for psychiatric morbidity, found a high incidence of depressive illness with no cases of schizophrenia encountered. In addition, those with prolonged depressive illness were the largest group to receive disability pensions. Hallert and Astrom [112] proposed that there is a strong correlation between celiac disease and depressive illness. Depression was hypothesized to result from decreased central monoamine levels secondary to nutrient deficiencies. Nutrient deficiencies were the result of intestinal malabsorption present in celiac patients. Hallert et al. [113] reported reduced lumbar cerebrospinal fluid (CSF) monoamine metabolites in untreated celiac patients. As stated previously, Sourkes [18] described the required dietary nutrients for monoamine synthesis (serotonin and catecholamines) as (1) the amino acids, phenylalanine or tyrosine, tryptophan, and methionine, (2) the vitamins, pyridoxine (B6) and ascorbic acid (C), and (3) the minerals, iron and copper. Decreased central nervous system levels of monoamines (serotonin and catecholamines) have been implicated in depressive illness [15,16].

In 1983, Hallert and Sedvall [113] determined the metabolites of central nervous system (CNS) monoamines from seven untreated adult celiac patients. Concentrations of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 4-hydroxy-3-methoxyphenylethylene glycol (MOPEG) (3-methoxy-4-hydroxy-phenylethylene glycol [MHPG]) metabolites of serotonin, dopamine, and norepinephrine, respectively, were determined by lumbar studies. In addition, the concentration of CSF tryptophan, the dietary precursor of serotonin, was measured. All patients were placed on gluten-free diets and when jejunal biopsies revealed the evidence of remission of the celiac disease, CSF studies of monoamine metabolites were repeated. Approximately one year (range 7 to 18 months) elapsed between the initial and final CSF studies. The results were significant for a mean increase of 33% in the concentrations of CSF monoamine metabolites, indicating increased central metabolism of serotonin, dopamine, and norepinephrine. CSF tryptophan levels showed an insignificant increase of 10%. The simultaneous improvement in the jejunal mucosa, together with significantly elevated CSF levels of monoamine metabolites in treated adult celiac patients indicated, according to the authors, that reduced central monoamine levels in untreated adult celiac patients may not be genetically determined. Instead, environmental factors such as a nutrient malabsorption may be involved.

Hallert et al. [112], employing the MMPI, evaluated the psychopathology of 12 untreated celiac patients diagnosed by history, biochemical signs of malabsorption, and jejunal biopsy. The celiac patients were tested on the MMPI (1) at the beginning of the study following diagnostic assessment for celiac disease, (2) after approximately one year on a gluten-free diet plus vitamin supplements (folic acid, three patients also on vitamin B12 and iron) with morphological evidence of improvement in the jejunal mucosa, and (3) after approximately three years on a gluten-free diet with 80 mg pyridoxine hydrochloride (B6) added 6 months before testing. The control subjects in this study were 12 surgical patients scheduled for elective cholecystectomy. Celiac patients exhibited a high score (greater than 70) on the depression scale of the MMPI on initial testing (70 ± 12.5), and
retesting on the MMPI one year following a gluten-free diet revealed no significant change on the depression scale (68 ± 14.0). No significant abnormalities were present in the other subscales including the schizophrenia scale in comparison matched with the control group. The third MMPI testing which occurred three years following the initial evaluation and included six months of B₆ supplementation revealed a significant drop in the depression scale to 56 ± 8.5 (p < 0.01).

The authors suggested a possible association between pyridoxine deficiency and the symptoms of depression reported in untreated celiac patients. Pyridoxine is a required nutrient in monoamine synthesis. It has been shown to be poorly absorbed in children with acute celiac disease [114]. Paradoxically, Hallert et al [110] found increased levels of pyridoxal phosphate (active B₆ coenzyme) in the CSF of untreated celiac patients; furthermore, an insignificant correlation between changes in both CSF serotonin and its dietary precursor tryptophan was reported in the previous study [113]. Further investigation into the role of the malabsorption of nutrients in the etiology of depressive illness seen in untreated celiac patients is needed.

It is possible that there may be two subgroups of celiac patients, one with a genetic vulnerability to develop schizophrenia secondary to gluten neurotoxins or exorphins, and another subgroup of celiacs with a genetic vulnerability to depressive illness who are predisposed to develop intestinal lesions resulting in the malabsorption of required nutrients for brain neurometabolism.

SECTION II: MAJOR DEPRESSIVE ILLNESS

INTRODUCTION

Depressive disorders have been recognized for many centuries. The term melancholia itself is Greek for "black bile" and is itself an ancient humoral hypothesis put forth to describe a severe form of this disorder. There have been multiple hypotheses proposed for the origin of this disorder, ranging the gamut of human experience and imagination. It is certainly not possible to review the history of the theories of this disorder. Indeed, it is most likely not a unitary disorder, but a spectrum of disorders with similar resultant symptomatology. Thus, biologically homogenous experimental human populations of depression do not exist. Differing etiological theories derive not only from experimental design, but also from the nature of the populations studied and the definition of the disorder used in selection of experimental subjects [115].

The past 30 years have seen a major expansion of our knowledge and understanding of the biochemistry of these disorders. The resulting neurochemical theories and neuroendocrine correlates of depressive disorders will be briefly reviewed by way of background for the main topic of this section, the nutrients and cofactors that may be involved in depressive disorders.

THE BIOGENIC AMINE HYPOTHESIS OF DEPRESSION

It has been known since the 1950s that certain drugs used in the treatment of hypertension can produce depression in certain individuals [116]. Reserpine precipitates depression in 15% to 20% of hypertensive human patients when given in doses of more than 0.5 mg daily. In a third of these patients the depression is serious enough to require psychiatric hospitalization. Similar depressive states have been produced by administering alpha methyl dopa [116].

Laboratory studies have shown that reserpine depletes normal stores of norepinephrine and 5HT by impairing their storage in intraneuronal granules and thus impairing their protection from degradation by MAO enzymes. Furthermore, alpha methyl dopa induces depletion of central catecolamines and 5HT through synthesis inhibition [116].

In 1952 iproniazide was found to produce mood elevation in tuberculosis patients receiving the drug experimentally as a potentially new antituberculosis agent [117]. Subsequent trials of this drug in depressed patients showed it to be effective in alleviating their depressions. This drug was found to inhibit MAO, the degradative enzymes that deaminate the biogenic amines norepinephrine, dopamine, and 5HT. Since then many more MAO-inhibitors (MAO-I) have been developed and are used as antidepressants; the degree of inhibition of MAO activity appears to be related to their clinical antidepressant efficacy [117].

Imipramine, another drug with antidepressant properties, was originally developed in the late 1940s as a possible antihistamine sedative or hypnotic. In 1958 during clinical investigation of this drug, Kuhn discovered that, unlike the phenothiazines to which it is chemically related, it was relatively ineffective in quieting agitation psychotic patients. Instead, it was found effective in some depressed patients. A subsequent search for additional chemically related antidepressant compounds led to the discovery of a number of new antidepressants in this group, the tricyclic antidepressants (TCAs) [118]. Further investigation revealed that imipramine and other antidepressants in this class block biogenic amine (dopamine, norepinephrine, 5HT) reuptake by the presynaptic neuron, a major mechanism of inactivation of biogenic amines at neuron synapses.
By the 1960s, the biogenic amine hypothesis was put forward as an experimental model based on the clinical effects of MAO-Is, the TCAs and alpha methyl dopa. This biogenic hypothesis stated that some depressions may be associated with an absolute or relative insufficiency of monoamines, principally norepinephrine or 5HT, at functionally important neural synapses in the brain [119-121].

This model was recognized as a probable oversimplification of the disorder at the outset, but it provided a useful heuristic model for further study. Since then, the evidence in support of this model has continued to accumulate.

We now know that in some depressions, urinary MHPG levels are abnormally low [122]. This compound is a metabolite of norepinephrine. Further, 5-HIAA (a metabolite of 5HT) is abnormally low in the CSF of some patients who have committed suicide by violent means that brain 5-HIAA has been found abnormally low in some patients who have committed suicide [123].

Not all depressed patients have low 5-HIAA or low MHPG levels, and the exact interrelationship between 5HT and norepinephrine is complex; therefore, it is not always possible to predict which antidepressant will work best based on urinary MHPG or CSF 5-HIAA levels [116]. Not only are absolute quantities of catecholamines at neuronal synapses implicated in the development of depressive disorders, but receptor sensitivities at these same synapses may also be involved. Neuronal receptors can be affected by a host of recently investigated factors in the CNS neurons, which we are only beginning to understand.

ACETYLCHOLINE

Acetylcholine in the CNS has also been implicated in some depressions [121,124]. It has been noted that physostigmine, a cholinesterase inhibitor in the CNS, can produce depressions in susceptible individuals, and there is mounting evidence of acetylcholine receptor supersensitivity in some individuals who are prone to depression. Further, physostigmine and other CNS cholinergic drugs can produce neuroendocrine changes similar to those seen in some depressions [121,124].

DEPRESSION AND THE ENDOCRINE SYSTEM

A number of endocrine system abnormalities appear to be present in certain patients with depressive disorders. The existence of depressive-like states in hypothyroidism and Cushing's disease and the recognition of postpartum depressions and the involuntional depressions all suggest an important linkage between the endocrine system and depressive disorders.

Cortisol hypersecretion, reflected in 24-hour urinary-free cortisol levels, has been found in approximately half of depressed patients [125,126]. This abnormality resolves when the depression clears; depressed patients showing this disorder fail to suppress cortisol when dexamethasone is administered. This nonsuppression points to central endocrine abnormality. Similarly, some depressed patients fail to increase TSH output from the pituitary when THRH is exogenously administered, as would normally be expected. It has been suggested that this nonresponse is due to chronic intrinsic hypersecretion of THRH, leading to down-regulation of the neuronal receptor sites responsible for TSH secretion [121,125].

Some investigators have reported abnormalities in the hypothalamic-pituitary growth hormone axis, including a reduced growth hormone response to insulin induced hypoglycemia in some depressed patients [121,125]. These results and their interpretation are actively being debated in the literature, and the significance of this finding remains uncertain at this time.

NEUROTRANSMITTER-ENDOCRINE RELATIONSHIPS

The neurotransmitters 5HT, dopamine, norepinephrine, and acetylcholine are also found in neurons that innervate the hypothalamus [43,125,127]. This may be of significance in furthering the understanding of the association between major depressive illness and the frequent depressive symptoms of appetite and weight changes.

Appetite regulation by the hypothalamic feeding and satiety center has been demonstrated in animal studies by stimulation and ablation of the hypothalamic nuclei representing these centers [42]. Changes in brain levels of monoamines, already implicated in depression, have also been implicated in appetite regulation of feeding and satiety states [128,129].

Therefore, it may not be necessary to see the endocrine abnormalities in depressive disorders as separate or distinct from the neurotransmitter abnormalities already described. It may be that the endocrine abnormalities are secondary to the neurotransmitter defects in some depressive disorders. The appetite disturbances seen in depressive illness, which are usually viewed as secondary manifestations, may in some instances be primary determinants of the disease process (see introduction). Currently, there is much controversy in the literature concerning anorexia and bulimia as separate and distinct diagnostic entities or variants of affective illness [130]. (See Chaitin et al, this volume.)

The interrelationship between depression and eating behavior needs further delineation. However, the im-
important role played by the brain monoamines appears evident. Nutrients influencing the synthesis of the monoamines and acetylcholine (dietary precursors, vitamin coenzymes, and associated biochemical factors) may be of heuristic value in the understanding of the biochemistry of depression and of clinical value in the use of a new treatment modality. This will be the topic of the next section.

**NUTRITIONAL AND DIETARY FACTORS IN MAJOR DEPRESSIVE ILLNESS**

A subgroup of patients with endogenous depression or major depressive illness may have functional deficits in brain monoamine (MA) metabolism, thereby involving serotonergic and catecholaminergic neurotransmission [16,121,125]. The amino acids tryptophan and tyrosine are dietary precursors for the synthesis of the central monoamines. Tryptophan is the substrate for 5-HT synthesis; tyrosine is the substrate for dopamine synthesis. In neurons containing the enzyme dopamine-beta hydroxylase, dopamine is metabolized to norepinephrine [8-12,131,132]. The role of the dietary precursors tryptophan and tyrosine in influencing the synthesis of the central MAAs and thereby altering behavior and mood has been investigated [131,133-138]. The mechanism coupling the brain concentration of tryptophan and tyrosine to the plasma availability of these nutrients has been determined largely from animal research [8-12,139], and this mechanism will be described briefly.

The brain uptake of the dietary precursors tryptophan and tyrosine depends on a low-affinity type transport system in which there is competition among the large neutral amino acids (LNAA) including tryptophan, tyrosine, phenylalanine, leucine, isoleucine, and valine for uptake into the brain. The factor facilitating the flux of tryptophan into the brain is an increased plasma ratio of tryptophan in relation to the other competing LNAA. The factor that increases the plasma concentration of tryptophan in comparison to other competing LNAA is the secretion of insulin, which is stimulated by a carbohydrate-rich meal. Approximately 80% of tryptophan is loosely bound to albumin, while 20% is free in the circulation. Insulin secretion shifts the LNAA to the peripheral tissues except for albumin-bound tryptophan, which then becomes more concentrated in the plasma than the other LNAA. This tryptophan, because of the relative depletion of the competing LNAA, becomes more available for uptake into the brain. Once across the blood-brain barrier, tryptophan can enhance serotonin synthesis, because the enzyme tryptophan hydroxylase is not usually fully saturated and readily reacts with the available amino acid substrate. Dietary manipulations employing tryptophan supplements taken together with a carbohydrate snack may act as a treatment strategy to increase brain serotonin production [11,140].

Tyrosine uptake into the brain is by the same low-affinity type transport system used by tryptophan. The enzyme tyrosine hydroxylase is also not saturated by its amino acid substrate, allowing for enhanced catecholamine (CA) synthesis. However, unlike tryptophan, where there is no known cerebral extracellular feedback mechanism to inhibit the synthesis of 5HT, CA synthesis and release is modulated by neuronal firing rates and amine turnover [8-12]. As stated by Gelenberg et al [131] "...in disease states characterized by deficiencies in norepinephrine or dopamine, in which neurons may be firing more rapidly (in an attempt to compensate for the deficiencies), there could be greater sensitivity of CA neurons to tyrosine administration." Theoretically, a subtype of endogenous depression mediated by decreased synthesis of norepinephrine may result in increased firing of catecholaminergic neurons as a compensatory mechanism. Under this condition of increased noradrenergic neuronal firing, tyrosine supplements may be employed to enhance norepinephrine synthesis.

Gelenberg et al [131] and Van Praag [133] reviewed the numerous controlled studies of tryptophan in depression over the previous decade. The results of these studies were inconclusive. The equivocal findings were explained by the following arguments:

1. The putative heterogeneity of depressive illness.

Theoretically, only those patients with decreased brain serotonergic activity should be positive responders to tryptophan supplementation.

2. A therapeutic window may exist for tryptophan in which certain limits of plasma tryptophan must be present for therapeutic effect. Exceeding or going below these limits may result in therapeutic failure. Tryptophan in a dosage above the therapeutic window may result in diminished plasma levels of its competitor tyrosine, which would lead to reduced CA synthesis [139]. Furthermore, a dosage of tryptophan above the therapeutic window may result in the greater induction of the liver enzyme tryptophan pyrrolase, which would increase the catabolism of tryptophan and, therefore, decrease the plasma levels of tryptophan.

Other possible factors for the inconclusive results obtained in earlier trials using tryptophan may involve the frequent lack of the administration of a carbohydrate-rich meal with tryptophan. As stated previously, a carbohydrate-rich meal or snack will facilitate the uptake of tryptophan into the brain. Also, there may be a subgroup of patients with a dysfunction in the transport car-
Further evidence in human studies of brain serotonin mediated behavioral changes associated with altered plasma availability of tryptophan was addressed by Branchey et al in 1984 [142] in which the tryptophan/LNAA plasma ratio was found to be significantly decreased in a subgroup of depressed alcoholics with a history of suicide and/or aggression. The relationship between decreased 5HT levels in depressives with a history of suicide and/or aggression has been reported previously [143].

Tyrosine, the precursor of dopamine and norepinephrine has been scantily investigated as a pharmacological treatment in depression. This may have been due to the former belief that tyrosine administration would not affect CA synthesis [131,138]. However, animal studies indicate that tyrosine may enhance CA synthesis under circumstances of increased neuronal firing and amine turnover (as previously discussed). Some initial data indicate a correlation between Tyroplasma levels and changes in depression, as determined by Hamilton Depression Rating Scale (HAM-D) [138]. Further investigation is needed.

The synthesis of acetylcholine, another neurotransmitter implicated in depression, may also be affected by its dietary precursor. Choline is a nutrient found in eggs, meat, and legumes in the form of lecithin and in milk in the form of sphingomyelin. Increasing brain choline levels by the administration of its dietary precursor lecithin may affect acetylcholine synthesis under circumstances of increased cholinergic neuronal firings similar to the mechanism proposed for tyrosine precursor control of the catecholamines [8]. The therapeutic employment of lecithin for precursor enhancement of acetylcholine synthesis is currently under investigation in the treatment of tardive dyskinesia, depression, mania, and several neurological diseases [8,140].

As Gelenberg et al [131] state in their review of neurotransmitter precursors in depression "...future studies on these substances would do well to incorporate important biochemical markers such as plasma amino acid levels, urine and possibly CSF amine metabolites, careful control of diet, and attention to optimal levels of drug dosages." In future studies on dietary precursor treatment response in depression, biochemical measures of the tryptophan and tyrosine to plasma amino acid ratios would be efficacious in treatment strategy; a low tryptophan/LNAA ratio may indicate selection of tryptophan, a low tyrosine/LNAA ratio may indicate selection of tyrosine, and a possible low plasma level of both tryptophan and tyrosine may indicate a combination of the two agents as a treatment strategy in depression. Correlating the tryptophan and tyrosine plasma neutral amino acid ratios with the urine and CSF amine metabolites to treatment response may provide additional supportive evidence for the dietary precursor con-
trol of monoaminergic synthesis and additional support to the monoaminergic theory of depression.

Pyridoxine, vitamin B_6_, among its diverse functions, is required as a coenzyme (pyridoxal phosphate) with the apoenzyme L-aromatic amino acid decarboxylase in monoamine synthesis [18]. Pyridoxine deficiency has been implicated in depressive symptomatology reported in females using oral contraceptives [24,63,144]. Adams et al [145], employing a double-blind crossover design, investigated 22 depressed women taking oral contraceptives for biochemical indices of vitamin B_6_ deficiency and clinical response to B_6_ treatment. In order to better correlate the symptoms of depression with the use of oral contraceptives, patients with a previous psychiatric history of endogenous depression and patients with current psychosocial stressors were excluded from the study. Patients with moderate to severe depression, as judged by a score equal to or greater than 23 on the Beck self-rated depression questionnaire were included in the study. The results indicated 55%, or 11 of the 20 depressed women, had biochemical evidence of an absolute (as opposed to relative) B_6_ deficiency, and this subgroup showed significant improvement to the administration of pyridoxine. The proposed biochemical mechanism of the depression observed in women taking oral contraceptives involved a possible alteration in amine metabolism as a consequence of B_6_ depletion. Pyridoxal phosphate depletion may arise as a result of estrogen conjugates competitively inhibiting pyridoxal phosphate binding to its apoenzyme. In addition, estrogen may stimulate increased cortisol production, which may induce increased activation of tryptophan oxygenase in the liver, thereby shifting tryptophan away from the brain to the peripheral tryptophan-kynurenine-niacin pathway [144,145].

Isoniazid (antituberculin drug), hydralazine (antihypertensive drug), and pregnancy have also been associated with vitamin B_6_ deficiency [63]. Neurobiological and psychiatric symptoms of B_6_ deficiency have been numerous, including depressive symptomatology (see section on Nutritional and Dietary Factors in Schizophrenia).

Depressed psychiatric patients have also been surveyed for vitamin B_6_ deficiencies [146-148]. Nobbs [146] found only 1 of 23 depressed patients to have conclusive evidence of pyridoxal phosphate deficiency and three additional patients to have suggestive evidence of deficiency. Stewart et al [147] assessed the plasma B_6_ levels in 101 consecutive outpatient psychiatric patients placed on depression treatment protocols; he found that 21 patients (21%) had abnormally low B_6_ values.

Patients were medically cleared before the study. Possible neurological symptoms associated with B_6_ deficiency including numbness, paresthesias, and subjective feelings of electric shock were also evaluated. Of 75 patients assessed for these specific neurological symptoms, 14 (19%) revealed neurological findings positively correlated with the B_6_ deficient group. As the authors state, “These data do not tell us whether diet, depression, or some other etiology accounts for the B_6_ deficits found. Other vitamin deficiencies should also be investigated in order to determine whether low B_6_ is an isolated finding in these patients or part of a larger picture of panhypovitaminemia.” Other researchers have proposed that pyridoxine may be associated with endogenous depression [148]. Multiple vitamin deficiencies in psychiatric patients have also been reported [149]. (For the role of wheat gluten and pyridoxine in depression, please see section on Schizophrenia and Wheat Gluten Enteropathy.)

Folic acid deficiency has also been associated in the literature with depression [78-80, 149-151]. There is evidence that folate-deficient rats and humans have decreased brain 5HT activity. Botez et al [152,153] found lowered levels of CSF 5-HIAA, the major metabolite of 5HT, in the folate-deficient patients who exhibited neuropsychiatric symptoms consisting of organic mental changes, polyneuropathy, and depression that were responsive to folate supplementation. The group unresponsive to folate supplementation did not show lowered levels of CSF 5-HIAA. Furthermore, in the folate-responsive group CSF 5-HIAA reverted to normal following folate treatment, indicating increased activity of 5HT. (Paradoxically, rats given excess folic acid also showed decreases in 5HT activity [152].) Exacerbation of psychiatric illness with excesses of folic acid has also been reported [154].

Folic acid-deficient rats have also demonstrated decreased levels of s-adenosylmethionine (SAM) [155], a physiological substance found in mammals interrelated with folic acid in transmethylation reactions [21]. SAM is the major “methyl donor” in methylation reactions involving brain neurotransmitters including monoamines [19]. SAM has been shown to have antidepres-ant properties [156,157].

The interrelationship between SAM and folic acid suggests an important metabolic link between folic acid and brain monoamine synthesis. It was mentioned in a previous section (see section on Other Biochemical Theories of Schizophrenia) that Osmond and Smythies in 1952 put forward the first modern biochemical hypothesis of the etiology of schizophrenia, the “methylation hypothesis.” The interrelationships between the folate cycle, s-adenosylmethionine, transmethylation, and the brain monoamines suggest that methylation processes may be implicated in affective disorders.
Folate deficiencies have been associated with the use of diphenylhydantoin (dilantin), oral contraceptives, barbiturates, and ethanol. Reynolds and Stramentinoli, reviewing previous surveys since 1967 of the serum folate levels of inpatient psychiatric populations, found 10% to 30% may have low serum folate levels most often associated with depression. Other reported symptoms of folate deficiency are organic mental states, psychosis, sleep disturbance, and mental retardation.

A study by Thornton and Thornton on serum folate values in 269 psychiatric hospital admissions controlling for dietary habits, medications, and gastrointestinal illness revealed a greater incidence of low serum folate in the psychiatric population. Chadirian et al. investigated folate values in 16 depressed patients, 13 nondepressed psychiatric patients, and 19 medical patients. Excluded from the study were patients with cancer, anemia, and gastrointestinal illness as well as patients taking medication known to affect folate levels. For one week before the study patients were placed on a standard hospital diet and were medication free. Results indicated that the depressed group had significantly lower serum folic acid levels than the other two groups. The authors suggested that depression due to folic acid deficiency may be a distinct entity, but further investigation is needed.

CONCLUSION

Brain neurometabolism can be dependent on the plasma availability of ingested nutrients. The fact that brain function can be affected by dietary factors gives importance to an investigation of nutrition, brain neurometabolism, and human behavior. Brain monoamine synthesis of the neurotransmitters serotonin, dopamine, and norepinephrine has been implicated in psychiatric illness through the "dopamine hypothesis" of schizophrenia and the "biogenic amine hypothesis" of major depressive illness.

Required nutrients in monoamine synthesis and other nutrients affecting monoamine synthesis through metabolic interactions were reviewed in the literature for their relationship to schizophrenia and major depressive illness—two psychiatric illnesses that seem to have strong genetic loading and investigated biochemical abnormalities. Other associated biochemical factors affecting appetite and body water regulation were also examined.

The data suggest that nutrients may be important factors in schizophrenia and major depressive illness. The role of eating behavior and body water regulation may also play an integral part, as the same neurotransmitters implicated in schizophrenia and major depressive illness are implicated in the neural-hormonal regulation of appetite and body water.

The role of nutrients in affecting human behavior and the effective use of these nutrients as a treatment or adjunctive modality in medical and psychiatric illness is as yet to be determined.

While this chapter has focused on certain specific nutrients, it is certainly possible that other chemical compounds currently known or as yet to be discovered may also play a major role in these disorders; certainly, the investigations reviewed in this chapter indicate that further research in the role of nutrition and human behavior should be actively pursued.

In addition to expanding this research into other chemical compounds, other neurobehavioral disorders may involve the same neurotransmitter systems already outlined in this chapter. For example, the authors are currently investigating the efficacy of tyrosine, an amino acid precursor to catecholamine synthesis, as a possible treatment for Attention Deficit Disorder of Childhood. In this pilot study, the response to treatment with tyrosine of ten prepubertal males diagnosed with this disorder will be correlated with biochemical measures (plasma amino acid levels and urinary MHPG levels), cognitive measures (Paired-Associate Learning Test), and behavioral measures (Conner's Rating Scale).

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