NEUROLOGICAL AND PSYCHOLOGICAL MANIFESTATIONS OF B VITAMIN DEFICIENCIES IN MAN

by

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B. S., Kansas State University, 1971

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1974

Approved by:

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INTRODUCTION

Recently it has been shown that nurtition during the prenatal period and postnatal development to four years of age, has a direct bearing on the development of an individual's nervous system and brain (1). Without proper nutrition, particularly nutrients such as protein and B complex vitamins, normal brain lipid, intellectual potential and metabolic functions are altered resulting in retardation of brain growth, nerve lesions, and other evidence of organic brain damage and neurological changes (2-4).

Facts have been presented in many studies relating the effects of poor nutrition during infancy, but what about poor nutrition after the developing years? What happens to the adult suffering from malnutrition--does his brain decrease in size, do neural lesions develop or does the intelligence level of the individual fall? It is in search for answers to these and many more related questions, that this review of literature has been undertaken.

A number of factors influence behavioral changes of the undernourished and deficient individual--environment, culture, society, and the availability of nutrients. In this paper we will be studying only the neurological implications of nutrient deficiency, and their relationship to possible changes in behavior. Sociological implications and methods of dietary treatment of such conditions will not be considered at this time.

NORMAL FUNCTION OF B-VITAMINS

What Are the B-vitamins

The B-vitamins are a complex of compounds characterized by their solubility in water. Hence their classification in the group of vitamins

known as water soluble. Essentially the B-vitamins are all interrelated in their function: functioning in aspects of protein, fat and carbohydrate metabolism in the cell (5).

Being classified as a water soluble vitamin indicates that they are not stored in large amounts in the body, are excreted in the urine and are rapidly depleted during deficiency (5). Sources of B-vitamins are primarily animal, such as meat, eggs and dairy products with enriched grains and grain products also containing significant amounts of the vitamins (6).

Included in the group of B-vitamins are thiamin (vitamin B_1), a sulfur-containing vitamin, riboflavin, niacin (nicotinic acid and nicotinamide), vitamin B_6 (consisting of a group of related pyridines: pyridoxine, pyridoxal, and pyridoxamine), pantothenic acid, biotin, vitamin B_{12} (cobalamin), folic acid (folacin), and choline, inositol and lipoic acid. The last three vitamins are believed to be necessary for human nutrition, but definite needs are not clearly established (6).

B-vitamin Function in the Body During Normal Nutrition

Thiamin

Thiamin or vitamin B_1, a vitamin readily soluble in water, is active in carbohydrate metabolism, through the co-enzyme co-carboxylase. Decarboxylation, which lead to the formation of CO_2, of α-keto and α-ketogeutaric acids is facilitated by the co-enzyme. Another co-enzyme, transketolase, is activated by thiamin and participates in the direct oxidative pathway for glucose (5).

Central and peripheral nerve cell functions are dependent upon the availability of thiamin in the diet (7). Nerve lesions of thiamin

deficiency may in part be caused by the antagonistic effect of thiamin with acetylcholine. (Acetylcholene allows transmission of nerve impulse from axon to dendrite making possible the contraction of muscles.) Thiamin is also essential to a normal appetite, good digestion and maintenance of muscle tonus of the gastrointestinal tract (7).

Myocardial function and nervous tissue are dependent on the availability of thiamin in the diet. Growth and lactation of animals, and possibly man, are also believed to be affected by the amount of thiamin provided. Thiamin, being essential to carbohydrate metabolism, is necessary for tissue respiration and activity and therefore essential in growth (8).

Riboflavin

Riboflavin-5-phosphate and its more complex flavin adenine denucleotides are coenzymes of riboflavin which combine with their apoenzymes to form many flavo-protein enzymes which are involved in the metabolism of carbohydrates, fats and proteins. These substances transfer hydrogen from niacin-containing enzymes to the iron cytochrome system, in turn forming water from oxygen and hydrogen and releasing energy within the cells (7, 8).

In man, riboflavin deficiency usually occurs along with deficiency of other B-vitamins; however riboflavin is important to maintenance of normal tissue and a deficiency will result in damage to much tissue (7). The eye is affected by riboflavin especially in light adaption. Respiration of poorly vascularized tissue, such as the cornea of the eye, is believed to be dependent upon riboflavin (8).

Niacin

Niacin or nicotinic acid is not only a vitamin but a direct link to an essential amino acid--tryptophan. Studies have shown that 60 mg. of the amino acid is readily and easily converted to the soluble amide form--nicotinamide.

Both niacin and riboflavin function as co-enzyme systems converting proteins and fats to glucose and subsequently oxidizing glucose to provide energy. By the removal of hydrogen ions the oxidation of glucose may take place in the absence of oxygen. The hydrogen ions are exchanged among simpler compounds, ending with oxygen as the final receiver and resulting in the formation of water (9).

Niacin deficiency affects many tissues due to a resulting deficiency of the niacin enzymes which are involved in the synthesis of protein. Excess amounts of nicotinic acid causes vasodilation, increased skin temperature, disturbances of pulse and heart rate and increases peristalsis (7).

Vitamin B_6

Vitamin B_6 is a class of compounds referred to as pyridines. Pyridoxine, pyridoxal and pyridoxamine are the compounds with all forms undergoing conversion to pyridoxal phosphate. Pyridoxine or B_6 is the name for the entire group. The most important and active form of the vitamin are the phosphate derivatives of pyridoxal and pyridoxamine. All three forms of vitamin B_6 are interconverted to the biologically active form pyridoxal phosphate within the body. In this form, pyridoxine is an active co-enzyme factor in many types of reactions in amino acid metabolism (9).

Cellular function depends on the presence of B_6 which functions as a co-enzyme for enzymes which decarboxylate many amino acids (7).

Transamination, the transfer of amine groups from one amino acid to another, is a reaction dependent upon B_6. Transamination allows the production of amino acids necessary for protein synthesis (8). Complete metabolism of tryptophan is dependent upon pyridoxal phosphate, and the formation of tryptophan from indole and serine is a reaction requiring the vitamin derivative. Glutamic acid, necessary in energy metabolism, is converted to γ-amino butyric acid, a regulatory factor for the neurons, found in the gray matter of the brain. This reaction is dependent on the availability of pyridoxal phosphate (9).

Metabolism of fatty acids, antibody production and endocrine activity involve pyridoxine as an essential constituent. Pyridoxal phosphate participates in the conversion of linoleic acid, an essential fatty acid, to aracadonic acid, another fatty acid. Tryptophan, an amino acid, is converted to serotonin, a neurohormone, with the aid of pyridoxal phosphate. Serotonin is a vasoconstrictor which stimulates cerebral activity and metabolism within the brain (7, 9).

Pantothenic Acid

Co-enzyme A, an essential in the metabolism of fat, protein, and carbohydrate, is a compound containing the vitamin pantothenic acid. The vitamin is necessary for all living organisms aiding in normal growth, normal development of the central nervous system and skin elasticity and suppleness (8, 5, 7).

Biotin

Biotin is believed to be essential to human nutrition, however a natural deficiency has never been observed. The vitamin is widely distributed

in foods, but when missing from the diet intestinal bacteria are able to synthesize it.

Biotin seems to be a part of many different functions. It participates in many biochemical reactions and transformations--deamination (removal of the NH_2 group), decarboxylation, synthesis of fatty acids and aspartic acid (an amino acid), and it is believed that it is involved in oxidation of glucose and metabolism of pyruvic acid (10).

Vitamin B_{12}

Vitamin B_{12} participates in the synthesis of nucleic acids and DNA in the bone marrow. B_{12} is referred to as the erythrocyte maturation factor, indicating that it is essential to the maturation of red blood cells which are necessary to the transport of oxygen to body tissues. When deficiency of B_{12} occurs, the number of red blood cells produced is lessened thus reducing the amount of available hemoglobin. Hemoglobin is necessary for bringing oxygen to the tissues and taking carbon dioxide from them (11).

Many of the functions of vitamin B_{12} and its co-enzymes are related to the folic acid co-enzymes in the body. B_{12} functions as a co-enzyme in reactions necessary for the production and further metabolism of tetrahydrofolic acid, and is essential for the formation of folinic acid co-enzyme. Within the developing red blood cells, functions dependent upon folic acid are in this way, indirectly controlled by vitamin B_{12} (12).

The nervous system is somewhat dependent upon the availability of vitamin B_{12} in the body. Vitamin B_{12} functions in nucleic acid synthesis in the changing of the carbohydrate ribose to deoxyribose. The protein bound vitamin is involved in the transfer of methyl groups, single carbon intermediates, from N^5 methyl tetrahydrofolate to the amino acid homocysteine

to methionine, an essential amino acid. Methionine can in turn be transmethylated to choline and serine can be formed by glycine.

Formation of pyrimidine bases and purine metabolism is dependent upon the presence of vitamin B_{12}. It is by this participation in the metabolism of purines and pyrimidines that B_{12} is involved in the synthesis of nucleoproteins and nucleic acids (12).

Folic Acid

Folic acid or folacin is found in many forms. Among these are pteroyltriglutamic acid and folinic acid. Folinic acid is a synthetic material.

The hemoglobin forming system in man is dependent on folic acid and its co-enzymes. It has a therapeutic effect on several types of anemia and reversible sprue. Without folic acid (which works with vitamin B_{12}) megaloblasts forms rather than normal red blood cells and the oxygen carrying ability of the blood is limited.

Nucleic acids and their formation are indirectly dependent on folic acid. Serine, thymine and purine bases are synthesized only when folic acid is present during some phase of the process. The amino acid homocysteine can be utilized in place of methionine if folic acid is present in the diet (7).

The following substances are not "true" vitamins, yet are related to vitamins in their activity.

Choline

The animal body can manufacture choline when needed, yet synthesis in man has not been proved. The vitamin is important in the synthesis of

protein, and in the animal body, two amino acids, serine and methionine, are used in the synthesis of choline.

Two fat related compounds contain considerable amounts of choline. Both lecithin and choline are phospholipids, the former being important in the metabolism of fat by the liver and the latter important in brain and nerve tissue. Choline helps to prevent accumulation of fat in the liver by having an affinity for the fat and in some way transporting it out of the liver.

Active acetate and choline combine to form acetylcholine, an important substance in nerve impulse transmission. It is believed that cell permeability is in some way influenced by acetylcholine (9).

Inositol

Inositol, it is thought, plays no specific role in human nutrition. Work with animals suggested that it helped to reduce the amount of fat storage in the liver; however tests on humans with cirrhosis of the liver proved otherwise (9).

ABNORMAL PHYSICAL CONDITIONS RESULTING FROM B-VITAMIN DEFICIENCIES

Deficiencies Resulting from a Dietary Lack

Thiamin is a vitamin, long recognized as important for "the maintenance of the normal urge to eat." For many years a proper appetite was recognized as the absence of a deficiency and the indication of the amount of thiamin in certain foodstuffs (13). Much of the early observations were made on test animals.

In all animals including man, the clinical manifestations are associated with changes in the central nervous and the cardiovascular systems. Loss of appetite appears to be the first significant observable symptom followed by loss of muscle tone, depression cardiac changes and the pathological syndrome beri-beri. As the disease continues, gastrointestinal changes occur and circulatory changes result in an enlarged dilated heart, edema and irregular cardiac rhythm. There is also increased sensitivity to noise and pain (14-16).

Because of impaired carbohydrate metabolism, the amount of glucose made available to the body systems is lessened. This is marked by decreased energy output and proper work performance. Animals fed diets rich in carbohydrate were shown to have a higher requirement for thiamin and when the vitamin was not available, death was usually the result (14).

Niacin deficiencies are usually observed where there has been a lack of the preformed vitamin and the amino acid tryptophan (where 60 mg. tryptophan equals one niacin equivalent). A lack of these substances results in the disease referred to as pellegra, characterized by dermatitis, diarrhea, stomatitis, and dementia. In pellegra sufferers there is a swelling of the tongue (glossitis) resulting in a burning sensation in the mouth. In other areas of the body, especially those where there is mechanical irritation and body secretions, there is usually evidence of body lesions. Mental symptoms also have been observed in patients with such deficiencies; these findings shall be discussed later in this paper (18, 17, 12).

Riboflavin deficiencies have not been well defined in man, however when they do occur the eyes, skin, nervous tissues and blood are most affected.

During deficiency in animals changes in the eyes such as corneal ulceration, cataracts, and dimness of vision and changes in skin resulting in scaliness and greasy dermatitis have been observed. Retarded growth and impairment of health may also occur during human deficiency (16-18).

Vitamin B_6 or pyridoxine deficiency symptoms include dermatitis around the eyes and chelosis, a condition marked by lesions in the angles of the mouth and lips. These symptoms, it is believed, are related to the role B_6 plays in the metabolism of the essential unsaturated fatty acids linoleic and linolenic into arachadonic and hexonic acids (17). Induced B_6 deficiency in man has confirmed the incidence of the above lesions and changes in the white blood cells without anemia have also been noted (14).

A deficiency of vitamin B_{12} is rarely due to a lack of dietary sources, however it has been known to exist among vegetarians who consume no animal foods what-so-ever. Persons such as these, examined in clinics have shown low serum levels of vitamin B_{12}, glossitis, paresthesias and some spinal changes without evidence of megaloblastic or pernicious anemia (19).

Folic acid deficiency is characterized by a lack of normal erythrocytes and is usually accompanied by extremely large erythrocytes. This nutritional macrocytic anemia is observed in a decrease in blood platelets due to alteration in blood manufacturing, reduction in leucocytes, glossitis and gastrointestinal disturbances. Both folic acid and B_{12} work together in prevention of certain types of anemia, therefore any deficiency of folic acid may also be closely related to faulty B_{12} absorption or utilization. The co-enzymes of vitamin B_{12} and folic acid are necessary for the synthesis of DNA. Without either of these substances, nucleoprotein synthesis is impaired, resulting in megaloblastic anemia. Vitamin B_{12} may provide

temporary relief from this type of anemia, however folic acid is necessary for complete recovery (14, 5).

A deficiency of pantothenic acid is considered rare in man and does not occur under normal circumstances. The vitamin is available in all foods known to man hence the name pantothenic which means "derived from everywhere." Experimental studies have induced a pantothenic acid deficiency in three subjects. Depletion of the vitamin has resulted in burning sensations in the feet, numbness and tingling of the hands and feet, cardiovascular instability, gastrointestinal disorders, infection and depression (14, 17, 18).

Biotin is needed in only minute amounts in the human diet, however a deficiency of the vitamin would invariably lead to death. Experimental deficiency can only be instituted by the addition of avidin to the diet or by ridding the intestine of biotin synthesizing bacteria through the use of antibiotics. Where the deficiency has been induced, however, scaling dermatitis and a gray pallor were some deficiency signs accompanied by lassitude, mental depression and muscle pains (10).

Deficiency of the vitamin choline is considered unlikely. Symptoms of cirrhosis, renal lesions, and liver scarring have been induced in laboratory animals. Choline is not really considered a vitamin for humans since it can be synthesized in the body by methylation of ethanol amine available from the amino acids serine and glycine. A combined deficiency of methyl donors and choline is the only way that a "true" choline deficiency can be induced.

It is believed that inositol is a substance which functions similarly to choline: it is a constituent of some phospholipids. Inositol deficiency has been induced in laboratory animals resulting in such symptoms as poor

growth and loss of hair. A natural deficiency is unlikely because of its wide distribution in foodstuffs. Little is known about its functions in human nutrition and more research is needed to determine its role as a vitamin or metabolite (10, 12, 18).

Deficiencies Due to Malabsorption

Rather than a dietary deficiency, B_{12} deficiencies are usually due to a defect in absorption. Malabsorption can be attributed to several factors: genetic, surgical or due to pregnancy.

Pernicious anemia is believed to be a disease of genetic origin in which the intrinsic factor is not produced. Because B_{12} cannot be absorbed, the bone marrow is unable to produce mature red blood cells. Instead there are a fewer number of large or macrocyted cells put into circulation. The result is a reduction in the ability of the cell to carry hemoglobin. Outward signs of pernicious anemia are observed in a lemon yellow pallor, loss of weight, and glossitis. Neurological manifestations are anexoria, unsteady gait, mental depression and parasthesias (10, 15).

Removal of parts of the stomach where the intrinsic factor, necessary for the absorption of B_{12}, is produced, or removal of any part of the illeum where absorption sites are located, will cause an increased susceptibility to megaloblastic anemia. A deficiency resulting from these procedures does not usually occur until three years or longer after surgery. Deficient absorption of vitamin B_{12} can also be the result of malabsorption syndromes such as sprue. In conditions such as these megaloblastic anemia does develop (14, 12).

In some instances where nicotinic acid has not been provided in the diet, but adequate tryptophan was available, deficiencies of the vitamin have still been observed. In these instances, tryptophan is usually metabolically diverted or inaccessible. Conditions include carcinoma, when proliferation of the abnormal cell type results in a conversion of 60% of the dietary tryptophan to serotonin (a chemical present in platelets, gastrointestinal mucosa, mast cells and carcinoid tumors. A substance quite similar in action to epinephrine.) Nicotinic acid deficiency can also be due to poor intestinal absorption of dietary tryptophan in Hartnup disease (an inherited disease manifested in defect of intestinal and renal transport of tryptophan, characterized by pellegra-like skin rash, cerebellar ataxia, and mental retardation). Altered amino acid levels of PKU and maple-syrup urine disease also cause a diminished efficiency in the use of tryptophan in producing niacin (20).

A familial disorder of pyridoxine has been observed in infants. It is characterized by seizures and a high daily vitamin B_6 requirement. This deficiency is rarely seen though because of its susceptibility to administration of vitamin B_6. Biochemical indications of the deficiency and metabolic manifestations have not been specifically observed in adults (12).

A folic acid deficiency can be caused by a poor intake, malabsorption, or by the use of antifolate drugs, including some anticonvulsants. In two families, unborn errors of folate metabolism have been observed causing megaloblastic anemia, ataxia, physical and mental retardation and convulsions. In these conditions there was an impairment in transportation of folate across both intestinal and cerebrospinal membranes (6).

NEUROLOGICAL AND PSYCHOLOGICAL CHANGES

Spinal Cord, Nerve and Brain Alterations

The adult brain is rich in many of the B-vitamins which function in numerous ways. As deficiencies progress, the level of nutrients in these tissues slowly decrease and processes which require these vitamins are in turn affected.

Manifestations of nutritional disease are widespread and occurring in nonspecific areas of the brain and nervous system. It has yet to be explained the reasoning behind damages, permanent or temporary, resulting from simple deficiencies. It is known that the brain, spinal cord and peripheral nerves may be affected in combination or singly. Many conditions such as degeneration of the spinal cord, peripheral neurites and multiple sclerosis may be stimulated by such deficiencies. The symptoms of such afflictions may appear due to deficiency rather than a true functional disorder (23).

When thiamin deficiency occurs in man, it usually manifests itself in changes within the nervous system. Varying degrees of deficiencies of thiamin result in differing disturbances within the nervous system. In sudden thiamin deprivation, there are gross neurological changes and death quickly ensues, as in beri-beri. Conditions such as Wernikes Syndrome where changes in the endothelium of the blood vessels cause increased numbers of pin-point hemorrhages, especially along the brain stem, are primarily due to grossly inadequate amounts of thiamin. And if deficiency is alternated with inadequate amounts of thiamin, neural lesions will appear (23).

Severe deficiencies of thiamin were first observed by Wernicke in 1881 (thus the name Wernickes' Syndrome; a condition, found often in old age or alcoholism marked by a loss of memory and disorientation), but it was not until later that it was definitely known that thiamin was a deciding factor in the disease. In later stages of deficiency, the peripheral nerves undergo structural changes along with changes in consciousness and irreversible damage to the cerebral structures. In the brain, lesions are found in and around the ventricular gray matter in terms of hemorrhaging, proliferation of blood vessels and glial cells with neuron degeneration (24).

The earliest of the neuromuscular diseases was defined as beri-beri, a thiamin deficiency disease, and because of this much more research has been conducted around this vitamin. Even though there is a large amount of knowledge concerning thiamin deficiencies, there have been few definite reasons for the increased susceptibility of the peripheral nerves to thiamin deficiency (25).

Early signs of biochemical changes in thiamin deficiency include hyperpyruvemia (excess accumulation of pyruvates) and decreased brain cocarboxylase (enzyme necessary for the oxidation of pyruvate). The thiamin pyrophosphate is the cocarboxylase and is also necessary for tissue metabolism. A defect in this energy metabolism system is thought to be the basis for neurological disturbances, because of the nervous systems' need for energy in its functioning. In test animals, it has also been shown that there is a significant decrease in the amount of glutamic acid produced in the brain, again relating to energy metabolism (25).

Signs of thiamin deficiency such as anorexia, depression, lassitude, loss of muscle coordination and partial paralysis could, in short, be

manifestations of the derangement of the nervous system. Post-mortem examinations in patients suffering from such symptoms, beri-beri, and animals in experimental avitaminosis have presented marked degeneration of the myelin sheath surrounding the spinal cords and peripheral nerves. Fatty acid, cholesterol, cerebroside and phospholipid content changes. Axons (nerve impulse transmitters) are destroyed, if they have not already suffered damage, and the neurons (the structural and functional units of the nervous system functioning in initiation and conduction of impulses) undergo the loss of their Nissl's bodies (21, 22).

In the disease of the peripheral nerves the primary site of disordered thiamin metabolism is the posterior root ganglion which in turn cause degeneration at the distal end of the axon. This fact has long been known since research has shown that the largest, and often longest, axons are first affected by a deficiency and in beri-beri the first signs of neural damage are usually in the areas most peripheral from the tropic nerve cell in the central and peripheral axons. It has also been noted that in severe thiamin deficiency, the distal part of the sensory and lower motor neurons suffer marked damage (26).

Niacin deficiency has been exhibited both experimentally and in the well known disease pellegra. This disease is encouraged by a lack of tryptophan, the precursor of niacin, and the absence of the vitamins thiamin, riboflavin and pyridoxine (27).

In experimental procedures, several groups of human subjects were subjected to a niacin deficient diet. In one study reported, in which the subjects were fed a corn diet deficient in preformed niacin and tryptophan, but adequate in other nutrients, both mild and severe deficiencies occurred.

The symptoms of deficiency were: dermatitis, glossitis, heartburn, abdominal pain, dysphagia and amenorrhea--all signs common in endemic pellegra also. Depression, anorexia and lethargy were also observed, but less frequently (28).

Nicotinic acid deficiency encephalopathy is an unusual disease of nicotinic acid deficiency, exhibiting none of the signs displayed in pellegra, but having severe mental and neurological changes. Involvement of the nervous system is first manifested in neurasthenia, followed by organic psychosis as seen by disorientation, impairment of memory and confusion. Even though the disease is observed as strictly a nicotinic acid deficiency, it has been seen in conjunction with thiamin deficiency, some symptoms of Wernicke syndrome and pellegra. This degenerative brain disease is characterized by clouding of consciousness, uncontrollable grasping and sucking reflexes and extreme rigidness of the extremities (26).

Prisoners of the Second World War were observed in many cases to be suffering from the effects of niacin deficiency. Pellegra was usually the result of the deficiency causing extensive and severe central nervous system damage, spasticity and brain changes. Onset and severity varies with the individual and has been studied extensively in India, a developing country plagued by nutritional disorders (28).

The Indians studied consumed a diet primarily composed of maize and exhibited clinical manifestations of pellegra with neurological manifestations of pyramidal and/or posterior columns. None of the subjects studied had manifestations of the peripheral nerves as is seen in thiamin deficiency. In two of one hundred and twelve patients observed the deficiency had become so severe that no improvement was seen when niacin therapy was provided.

This illustrates the irreversible, permanent damage that does occur if the disease goes untreated for a length of time (29).

Changes in the Nissl bodies of the cells are referred to as retrograde degeneration and include central chromatolysis, degeneration of the large neurons of the motor cortex, brain stem and anterior horn of the spinal cord. The above changes given are morphological lesions as seen in chronic pellegra (30).

Riboflavin deficiencies are seen in man, but neural tissues are not as sensitive to the lack of riboflavin as they are to other B-vitamins. Signs of the deficiency are classically seen in changes in the skin, outer covering of the eyes and the mouth. Women fed a test diet extremely deficient in riboflavin failed to develop neurological symptoms. In later studies, both man and animals deficient in riboflavin exhibited lowered physical activity and appetite followed by sudden collapse and coma (31).

In dogs, severe riboflavin deficiency causes fatty infiltration and yellowish color of the liver along with the above mentioned afflictions. It is believed that biochemical disturbances in the body produced blackening and degeneration of myelin sheaths in the brain and spinal cord and peripheral nerves. Many symptoms are thought to be similar to changes observed in human pellegra, but unlike thiamin, induces black tongue in dogs (21).

Avitaminosis B_{12} can be manifested in changes of the neurological processes without subsequent changes in the blood or bone marrow as are seen in pernicious anemia. In many instances abnormalities of the mental processes may dominate in the clinical investigation of pernicious anemia, and without treatment will often lead to physical changes within the nervous system (32).

Evidence that avitaminosis B_{12} may cause irreversible brain damage is conclusive. Brain lesions similar to those occurring in the spinal cord and in degeneration of the white matter of the cerebrum are seen in those suffering from pernicious anemia. Partially reversible EEG changes and reduced cerebral oxygen and glucose have also been observed (21).

The exact biochemical basis for neurologic lesions in pernicious anemia is unclear. Abnormal propionate metabolism in the nerves of subjects with pernicious anemia may possibly result in neural lesions. The myelin lipids surrounding nerve tissue turn over at a rapid rate and require the synthesis of normal fatty acids. It has been suggested that deranged fatty acid synthesis may be the basis for neurological lesions due to abnormal myelin (32).

One study reported suggests that deranged fatty acid metabolism may result in neurologic lesions. Nerve tissue samples were tested and observed from patients exhibiting B_{12} deficiencies and individuals having no clinical signs of vitamin deficiencies, illnesses or anemia. Nerves of those patients with pernicious anemia contained fewer fatty acids than those of the control group and two fatty acids of the anemic patients were abnormal odd chain fatty acids. One explanation for these changes has been offered. The metabolism of methylmalonyl-CoA is blocked in vitamin B_{12} deficiency resulting in an accumulation of the substance. A B_{12} co-enzyme is required for conversion of methylmalonyl CoA to succinyl CoA. Methylmalonyl CoA is a resulting product from the carboxylation of propionate or the degradation of certain amino acids. The accumulated methylmalonyl CoA might replace malonyl CoA in fatty acid synthesis causing synthesis of fatty acids with 1-carbon branches instead of straight chain fatty acids. The reduced fatty

acid and abnormal fatty acid production can result in myelin alteration or dysmyelinization in turn causing neuron function defects (33, 35).

Folic acid deficiency is often observed in patients admitted to psychiatric hospitals, elderly persons and individuals with various psychiatric syndromes. Folate deficiency is observed in individuals not suffering from anemia, however the most common deficiencies are observed in subjects suffering from megaloblastic anemia (33, 34).

The adult nervous system is highly resistant to folic acid deficiency although it is not impossible to develop neurological changes due to avitaminosis. Folic acid has been found in large amounts in the cerebrospinal fluid, in much greater amounts than what is found in blood serum, which suggests that folic acid is important to the nervous system (34).

One subject observed was grossly deficient in folic acid and had become ill with megaloblastic anemia and acute encephalopathy. Myelopathy was observed in another patient who, when treated with anticonvalsants, became deficient in folic acid. Other instances of peripheral neuropathy and myelopathy with confirmed neuro-pathological findings have been noted in the deficiency (34). Most symptoms reported in medical literature however, are related to behavioral or psychiatric changes which occur in individuals suffering from megaloblastic anemia or folic acid deficiency. These findings will be discussed later.

Natural pyridoxine deficiency due to a faulty diet in humans is very rare, but experimental deficiency has been induced in volunteers. Skin, mucous membranes and nervous tissue were the primary sites affected. Many patients exhibited emotional changes and peripheral neuritis (36).

In the brain, pyridoxine co-enzymes are essential to many enzyme systems. Evidence has been presented indicating that a deficiency of the vitamin created disturbances in the metabolism of neural lipids of the myelin sheath. Epeleptiform seizures are one of the results of deficiency as seen in man and experimental animals. The seizures may be accompanied by lesions of the brain and central nervous system, especially the cerebral cortex. Observed changes in brain chemistry due to pyridoxine deficiencies are: elevated cholinesterase activity, impairment of production of bound acetylcholine and deficient potassium content. These changes, leading to seizures, are believed to be due to changes in the production and utilization of cellular energy (37).

Pyridoxine deficiencies have been demonstrated in alcoholics and animals receiving antimetabolites. In tuberculosis patients receiving convulsant hydrazides, there has been increased excretion of pyridoxine leading to sensory neuritis and convulsions. Pyridoxal-5-phosphate combines with hydrazides to form hydrazenes and will inhibit the action of enzymes in which pyridoxine function. Glutamic acid metabolism in pyridoxine deficiency is inhibited and production of GABA (γ aminobutyric acid) is decreased. It has been postulated that reasons for neurological problems in pyridoxine deficiency are that pyridoxal and its derivatives function in the nervous system as it does in ascitic cells through amino acid and alkali metal in transport (36).

Pantothenic acid occurs widely in nature and a natural deficiency is unlikely. Producing experimental deficiency is the only way of observing its effects on man. In experimental procedures using laboratory animals, pantothenic acid deficiencies have provided some change in the nervous

system, but only after a long period of deprivation. These changes involved coma, paralysis and convulsions. In autopsies performed in these animals, well-defined lesions were observed on the peripheral nerves and spinal cord (36).

Experiments carried out in human subjects proved to be acute and severe in terms of stress and physical changes. Certain neuromotor disorders did appear along with gastrointestinal complaints, repeated infections and physical and mental complaints. Neurologic changed included numbness and tingling of the hands and feet; one subject also complained of burning feet. Weakness of extensor muscles and hyperactive deep tendon reflexes were present in the subjects. Biochemical changes consisted of alteration in acetylation, increase in insulin sensitivity, decreased response of eosinophile to ACTH and decreased hydrochloric acid production in the stomach (38).

Natural biotin deficiency is unlikely in man since it is available through intestinal synthesis, but it has been produced experimentally in man and other animals. Human subjects maintained on a diet of egg whites, which carry the biotin binding avidin, developed dermatitis, anorexia, lassitude, muscle pain and EEG alterations. Other neural symptoms were not observed (39).

The nervous system of humans contain large amounts of choline in the form of acetylcholine, and related compounds. Even though this vitamin is essential to the nervous system in these forms, little evidence has been provided to show that a deficiency will result in damage to the system. Human studies have not been observed, however in animals such as dogs and swine, deficiency has been induced. Changes occurring in these animals do

not indicate neurological manifestations but rather fatty infiltration of the liver, renal lesions, anemia, edema, neoplasma of the organs, decreased plasma protein and cellular necrosis (27).

Inositol is a substance which can and has been isolated from the brain and is the most actively metabolized of the cerebrospinal fluid at several times its blood level. It is a phosphatide and is believed to function similarly to choline. It is necessary for growth of yeasts, mice, rats, guinea pigs, chickens and turkeys; however no specific role in human nutrition has been defined. Experimental animals fed an inositol deficient diet develop eye defects, lose hair and are retarded in their growth (21, 40, 41).

Behavior and Mental Process Changes

Animals submitted to severe malnutrition show along with other changes, compromise of the central nervous system with changed water and lipid content, and protein synthesis (24). Malnutrition is considered to be a biological resultant of complex social, cultural and economic factors. But more important, it also encompasses starvation or total lack of food or when dietary intake of nutrients may be inadequate (32). Malnutrition includes diets deficient in vitamins and as we are interested in here, the B-vitamin complex vitamins. This absence of B-vitamins alone and their behavioral consequences is the factor we are most concerned with in this paper.

In nutritional stress behavior does change; however, the pattern of changes is different with each nutrient deficiency. Some cause impairment of sensory functions, others motor function (some permanent, due to lesions, some temporary) and also personality (24).

A study of the effects of a B-complex deficiency in man in which intellectual and motor functions and personality were markedly altered, identified thiamin as a crucial factor in maintaining a healthy nervous system (42).

One experimental group, composed of young adult men, was maintained on a thiamin free diet from two to four weeks. The sensory and motor functions of the subjects began to deteriorate in many instances. As the deficiency progressed they began to show such symptoms as anxiety, depression, irritability and increased sensitivity to noise and pain. The speed of coordinated hand eye movements was impaired along with reaction time. In this study, the areas not affected were strength and capacity for and recall of knowledge. Personality, however was changed remarkedly, indicating depression, as mentioned above, and also hypochondriasis and hysteria (43).

Another study provided data on individuals suffering from acute thiamin deficiency who were maintained on thiamin free diet. This experiment had consisted of four periods: a) 1 month of standardization; b) 168 days of partial thiamin restriction; c) a period of acute thiamin deficiency; d) a 9 to 21 day period of a thiamin free diet supplemented with 5 mg. thiamin (44). The first sign of malfunction in the subjects was vomiting. Following this symptom were anorexia and nausea, the first "functional signs" of thiamin deprivation. Psychiatric findings, such as weakness in the legs, paresthesias and tenderness of the trunk and muscle nerves, were particularly profound in the individuals who received no thiamin supplement during the period of partial restriction. Loss of coordination and muscle weakness were so intense in one subject, he was unable to raise himself and stand from a squatting position. Body sway was increased during thiamin deficiency and pattern tracing movements or eye hand coordination showed deterioration.

Speed of motion was reduced in the subjects along with speed of reaction time (45).

Pellegra is a deficiency disease characterized by loss of recent memory, lassitude, delusions, apprehension and depression. The disease is due to a deficiency of niacin and its precursor tryptophan and is not caused by multiple deficiencies. However, some of the same signs, without the drastic changes in body composition, can be exhibited in simple niacin deficiencies (46).

Deficiencies have been described in experimental animals and man when diets low in tryptophan and nicotinic acid have been used. Along with physical signs of deficiency (dermatitis, glossitis and diarrhea), subjects on niacin deficient diets developed mental depression and apathy (47).

As niacin deficiency progresses, changes in mental processes, which lead to the dementia known in pellegra, include confusion, dizziness, poor memory, and, as mentioned before, depression. The more severe results of the deficiency as are usually seen in pellegra include violent psychotic changes characterized by hallucinations and delusions of persecution (46).

In India a study of psychiatric changes in pellegrans was undertaken. Some cases of pellegra were manifested in psychiatric aspects rather than physical, and upon admission to mental hospitals, diagnosis revealed the deficiency disease. Certain geographical regions in India that have a high incidence of nutritional deficiency report large numbers of hospital admissions due to pellegra (32).

Psychiatric manifestations in pellegra develop slowly revealing only subtle changes at first and then progressing to more severe states as deficiency continues. Early signs observed include anxiety, weakness,

headache, lack of energy and difficulty in concentration. In acute deficiency, psychiatric changes were delirium, catatonia, acute and chronic schizophrenic like behavior, maniac or paranoid ideas and organic brain syndromes (29).

No clearly defined symptoms of nervous system disturbances have been identified with riboflavin deficiency in man. Eighteen women fed a diet deficient in the vitamin had no neurological or psychiatric changes, but did develop other outward symptoms characteristic with riboflavin deficiency (48, 19).

Mental confusion is one resulting change in avitaminosis B_{12}. It has been known for many years that pernicious anemia, resulting from a B_{12} deficiency, is associated with various mental symptoms. Some cases have gone without diagnoses for many years before finally being recognized through definite pernicious anemia. In case reports, patients who have severe mental symptoms such as depression, dementis and disorientation have been studied and many of their symptoms related to B_{12} deficiencies (19).

The most frequent psychiatric symptoms in pernicious anemia are depression, anxiety, loss of libido, irritability, poor concentration, and impaired memory. One study of 22 patients from the age of 11 to 60 years, revealed that psychiatric symptoms were present in 82 percent of those with pernicious anemia. The presence of these symptoms were unrelated to age, duration of illness, physical complications of physical illness or neurologic involvement (49).

In a general medical clinic fourteen women were studied and found to have low serum B_{12} levels without anemia. These women complained of nervousness, fatigue, malaise and depression. Their hemoglobin levels were

normal, therefore the psychiatric complaints were found to be unrelated to iron deficiency. It was concluded by this study that psychiatric complaints, depression anxiety and irritability, may be the result of an undetected B_{12} deficiency (49).

Folate deficiency in psychiatric illness has lately drawn considerable attention. More psychiatric patients with low serum folate levels have been observed in recent years and they were found most commonly in depressed patients. Reasons for low folate levels, among both the affluent and low economic groups, are psychological factors, increased alcohol consumption and barbituates or anticonvulsants. Nutritional folate deficiency can easily be induced in individuals (16).

Low serum folate levels contribute to the development of mental symptoms in epileptic patients, those suffering from depressive illness and alterations in personality traits. Patients observed with low serum folate levels exhibited higher depression inventory scores on admission and discharge from a clinical investigation ward than did those with normal levels. Validity scores were also low in patients with low serum folate levels and discharge neuroticism scores were higher than in the patients with normal serum folate. The validity and neuroticism scores are evaluations of changes in personality traits. Validity is an area of personality related to drive and psychic energy (32).

Folate deficiency, as like B_{12} deficiency, can exist in the absence of anemia. It is thought that some individuals may possess a lower physiological threshold when it comes to folate deficiency and therefore may be neurologically and psychologically affected more than others. Studies have shown that folate deficiency may be important to the adult nervous system,

but much individual variation has been observed. A study on one human volunteer revealed that severe symptoms of neurologic damage does not occur, but since forgetfulness, sleeplessness and irritability did result, a more marked abnormality may occur if the individual is more susceptible or the disease more chronic (35).

As noted before, pyridoxine deficiency can be induced experimentally in man. Most symptoms, however, are related to dermatitis. Since pyridoxine is necessary for the formation of active brain substances, serotonin and γ-aminobutyric acid, the vitamin may have a place in the control of related neurological conditions, but no definite evidence has been established. Some complaints of anorexia, nausea and drowsiness have been recorded (33, 9).

Requirements of vitamin B_6 have been seen to be unusually high in a small percentage of the population. Change has been observed more often in children receiving diets deficient in the vitamin. Severe deprivation has resulted in convulsions and seizures. In new born infants intractable seizures have also been observed when the mother is severely malnourished. Other symptoms have included mental retardation and muscle spasms (19, 33).

Pantothenic acid has caused inability to learn in experimental animals. In man however, there has been little observed in the way of psychiatric changes. Burning feet syndrome and some mental complaints were reported, but no marked changes in behavior notes (33).

Biotin, like pantothenic acid has been related to the inability of animals to learn. In experiments on human subjects, anorexia, lassitude, and sleeplessness occurred in biotin deficiency. Other symptoms of psychiatric change in biotin deficiency have not been recorded (33, 50, 35).

Choline deficiency results mainly in physiologic changes in various species. In swine, however, deficiency will create poor locomotor coordination. Further studies on the relationship of the nutrient in human deficiency is needed (51).

Inositol is another vitamin in need of further research. Rats and mice show a need for the vitamin in growth as mentioned before. Human cells require inositol for function, but direct relationship to the nervous system and emotional health has not been established (21).

THERAPEUTIC APPLICATION OF B-VITAMINS IN PSYCHIATRIC ILLNESS

A new concept in the treatment of mental illness has evolved in recent years. Much of this has come about because of the new understanding of the relationship of vitamins to neurologic and psychologic health. Many research psychiatrists believe that some individuals' diets cannot fulfill excessive requirements for a certain nutrient necessary for optimum mental health. If that nutrient is absent from the diet, psychiatric symptoms, it is felt, will develop. The above mentioned class of individuals may be treated with megavitamin therapy, using large doses of niacin, thiamin, folic acid or B_{12} and exhibit marked improvement in their mental capacity and behavior (52).

Large doses of thiamin and other B-vitamins given to alcoholic patients suffering from severe B-vitamin deficiency have provided remarkable improvement in behavior and attitude. This method is often used as routine procedure upon admittance of an alcoholic to a psychiatric hospital, because of an existing deficiency and oftentimes observable alcoholic pellegra and beri-beri (53, 13, 54).

Studies in India have shown that neurological and psychological manifestations in pellegra can be significantly improved with niacin therapy. Depression, anxiety, schizophreniform psychosis, dementia and neurasthenia regressed in 86.3% of 22 patients provided niacin. Of 112 patients treated for neurological manifestations, including parasthesia and convulsions, 110 recovered almost entirely (31, 49).

Depression associated with oral contraceptives and in premenstrual tension states has been successfully treated with pyridoxine (33).

Folic acid deficiency is another common occurrence in geriatric patients and treatment of what was believed to be psychiatric and neurologic complications due to the avitaminosis proved successful. In 2 cases of severe dementia, treatment with folic acid improved the mental state of one patient and caused complete recovery of another (55).

When vitamin B_{12} treatment for pernicious anemia is given, mental status and EEG improve as does cerebral oxygen consumption (55). In 6 individuals treated for deficiency and mental illness, 2 recovered entirely with improved neurological symptoms and a third showed marked mental improvement (56).

Clinical evidence of the treatment of schizophrenia indicates that niacin is an effective agent. Several cases where niacin therapy was used showed complete remission of schizophrenia and absence of symptoms for over ten years. Double-blind experiments testing large doses of niacin have also given researchers further encouragement in using the vitamin for certain degrees of psychosis and schizophrenia (52).

The above mentioned examples of successful treatment of psychiatric changes with B vitamins are only a few of the available examples. From

these cases though, it can be concluded that vitamin therapy, specifically B-vitamins, provide an encouraging avenue of treatment for those who are mentally ill.

SUMMARY

Vitamin deficiencies are still a very real part of our world and always will be. Deficiencies can be the result of faulty diet, malabsorption or total absence of food. The B-complex vitamins have been found to be necessary for the proper functioning and health of the human nervous system. Without these vitamins, deficiencies result, creating nervous system disorders, cardiovascular changes and physical complications. In the case of thiamin and niacin, the diseases of deficiency are manifested in changes in psychological and neurological systems of humans. Riboflavin, folic acid, vitamin B_{12} and other B-complex vitamins known to be essential to man, play important roles in behavior and neurological functions, but the exact knowledge of the extent of their role in behavior and neurological systems is not clearly understood. A review of literature pertinent to this subject has afforded many interesting data and theories to the function and need for these vitamins. Practical application in therapeutic settings has indicated certain psychological disturbances can be corrected through mega-vitamin treatment and increase the recovery rate in such individuals.

ACKNOWLEDGMENTS

I wish to thank Dr. Lucille Wakefield for her constant support and advice during the preparation for and writing of this paper and to Miss Beatrice Finkelstein and Dr. Albert King, for their constructive and beneficial review and evaluation of the material.

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NEUROLOGICAL AND PSYCHOLOGICAL MANIFESTATIONS OF B VITAMIN DEFICIENCIES IN MAN

by

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B. S., Kansas State University, 1971

AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1974

Vitamin deficiencies are still a very real part of our world and always will be. Deficiencies can be the result of faulty diet, malabsorption or total absence of food. The B-complex vitamins have been found to be necessary for the proper functioning and health of the human nervous system. Without these vitamins, deficiencies result, creating nervous system disorders, cardiovascular changes and physical complications. In the case of thiamin and niacin, the diseases of deficiency are manifested in changes in psychological and neurological systems of humans. Riboflavin, folic acid, vitamin B_{12} and other B-complex vitamins known to be essential to man, play important roles in behavior and neurological functions, but the exact knowledge of the extent of their role in behavior and neurological systems is not clearly understood. A review of literature pertinent to this subject has afforded many interesting data and theories to the function and need for these vitamins. Practical application in therapeutic settings has indicated certain psychological disturbances can be corrected through mega-vitamin treatment and increase the recovery rate in such individuals.