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Vitamin B-1 deficiency during pregnancy

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VITAMIN B-1 DEFICIENCY DURING PREGNANCY

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INTRODUCTION

Pregnancy is a normal physiologic process, but it makes special demands of the maternal organism. In a way it may be considered an efficiency test. Constitutional weaknesses may become evident under the additional strain of pregnancy, and a diet adequate under normal conditions may prove inadequate due to the increased requirements. Thus, pregnant women are likely to show dietary deficiencies more clearly than non-pregnant women. In the past too much emphasis has been devoted to the infecting organism as the cause of disease in maternal morbidity and mortality without paying proper respect to the health and resistive powers of the host. Then, too, there has been the tendency to relate disease as caused by the positive effect of something rather than regard it as the result of a lack of something upon which the organism is dependent.

Vitamin B-1 deficiency during pregnancy, as the etiological factor of pathological conditions, had not been recognized until the present time. Instead, polyneuritis, which was the most viscious offender, was observed to follow excessive vomiting in the early months of pregnancy and was considered a manifestation of toxemia (1,2,3,4). Likewise, many of the pathological

conditions occurring during pregnancy were thought to be results of some toxemia, recovery from which could be obtained by therapeutic abortion. At this point, however, it might be stated that none of these so-called hypothetical toxins have been identified. Formerly, the anemias of pregnancy were considered to be due to some toxic condition, but from the evidence of recent investigation they now arise from a lack of vitamin B-1, iron, and related elements (5). Recently, however, the great similarity between the degenerative nerve changes noted in polyneuritis of pregnancy and those found in beriberi has suggested the possibility that it might also be due to a dietary deficiency (6,7). Wide acceptance of deficiency as the primary factor was deferred until Strauss and McDonald (6) reported successful treatment of three cases of neuritis of pregnancy by diets rich in vitamin B. Further, their findings are supported by tha analogous findings that are observed in Korsakoff's Syndrome, which is now regarded as a vitamin deficiency, based on chronic alcoholism.

HISTORY OF VITAMIN B-1 AND VITAMIN B COMPLEX

Vitamin B-1 stands unique in that the present vitamin theory was first conceived and developed from studies on the antiberiberi factor and in that the class name was derived from early work on its chemical nature. From the epoch making investigations on beriberi in the Dutch East Indies by a group of Dutch medical officers starts the story of this important vitamin. Eijkman (8) discovered that the disease could be produced experimentally in fowls, and Grijins (10) theorized that the disease was due to a nutritional deficiency and not to toxicity or infection, thereby laying the foundation for the present day conception of the vitamins. A series of papers were published by Funk (11) in 1911 stating that a substance active in the cure of beriberi had been isolated from rice polishings. He stated the following year that: "The deficient substances, which are of the nature of organic bases, we will call 'vitamines'; and we will speak of a beriberi or scurvy vitamine, which means a substance preventing the special disease." Because of this, several nutritional deficiency diseases were placed in a separate class.

In attempts to ascertain the nature of all dietary

essentials, Hopkins (12), Osborne and Mendel (13) and McCollum (14) provided evidence that certain previously unidentified factors were necessary for the growth of rats. The name, "water-soluble B", was proposed by McCollum (15) for one of these factors and evidence was presented to indicate that the water-soluble B and the beriberi vitamine were similar in nature. Until 1920 the terms "beriberi vitamine", "water-soluble B", and "antineuritic vitamine" were used. It was then that Drummond (16) made the suggestion that the "e" be dropped and that the various substances be spoken of as Vitamin A, B, C, D, etc. At the present time this simple scheme should be quite sufficient until the different vitamins are isolated and synthesized so that their chemical structure can be determined and named more scientifically.

Prior to 1920 (17) the opinion with respect to the identity of the water-soluble, growth-promoting substance for the rat and the beriberi vitamin was not unanimous. The development of the existence of a complex of important substances was discovered experimentally largely after that date. The first investigation indicating that they should be considered different factors was reported in 1920 by Emmett and Luros (18).

Vitamin B was established distinctly as not a single chemical entity in several papers published by the United States Public Health Service. Goldberger and Tanner (19) proclaimed that pellagra was a dietary deficiency disease and the addition of brewers' yeast to the diet would prevent it. The name, "pellagra-preventive" or "P-P factor" was proposed by them for this dietary essential. The discovery by Smith and Hendrick (20) that yeast which had had the antineuritic vitamin in it destroyed by the action of the autoclave had a definite supplementing value in a diet for rats in which oats or Seidell's vitamin B picrate was the source of vitamin B. Goldberger and his associates (21) in a paper on the pellagra preventives in relation to vitamin B stated: "In any event, investigators using the rat-growth test must hereafter recognize and take due account of at least two essentials (B sensu stricto and P-P) where heretofore only one was considered." A pellagra-like syndrome was produced by Lillie and Goldberger (22) in rats using a ration to which adequate amounts of the antineuritic vitamin had been added. The prevention or the cure of this condition was accomplished by the inclusion of small quantities of autoclaved yeast in the ration.

The isolation of the antiberiberi vitamin was announced by Jansen and Donath in 1927 (23). The researches of Williams (24) elucidated the structure of the compound and shortly after that the synthesis was accomplished (25).

PHYSIOLOGY OF VITAMIN B-1

Vitamins are indispensable as they are needed for the metabolism of carbohydrates, proteins, fats, lipoids, and other substances; for the mechanism of biochemical oxidations and reductions; for the immunity reactions; for metabolism of cell nuclei (26).

The heart, liver and kidney were found to have the highest content of vitamin B-1 according to the feeding experiments performed with the tissues of normal and B-1 deficient rats (27). The liver and the kidney evidently act as storehouses for the dietary factor. Except the brain, every organ, including the heart, liver, kidneys, muscle, lung, spleen, stomach and intestine became thiamin-depleted after only five weeks on the deficient diet. Graham and Griffith (28) claimed that the rapid loss of thiamin, under such dietary conditions, had no analogue with respect to components of the vitamin B complex, assayed as a whole. The capacity of any organism to store vitamin B-1 is limited. This conclusion is supported by the amounts of the vitamin found in the various tissues under different dietary regimens. A period from ten days to three or four weeks is necessary for the shortage of vitamin B-1 to become evident in the pigeon, rat, and dog, the latter

period being characteristic of the largest of these species, the dog. Obviously, this limited capacity for storage is of great importance not only in relation to clinical situations but also in practical dietetics and hygiene as well.

Brodie and MacLeod (29) reported that the liver in animals living on a normal diet contained ten times more vitamin B-1 than voluntary muscle; the kidney was one-half and the brain one-third as rich per gram as voluntary muscle. The liver and heart are about equal in their vitamin B-1 content, and vitamin B-1 is found in traces in the blood, spleen and lungs. Also the intake of vitamin B-1 influences quite extensively the amount that is in the body.

The presence of vitamin B-1 in the urine is easily understood because the substance is water-soluble. The amount present varies with the intake, and it is markedly increased in diuresis (30). The findings of Harris and Leong (31) raises the presumption that the diet contains less than normal amounts of vitamin B-1 if the daily excretion is less than 12 I.U.(average 1 I.U. per 100 cc. urine). With the isolation and synthesis of pure vitamin B-1 and the perfection of microchemical methods by which to analyze the urine for this

factor, it is likely that a vitamin B-1 function test will be devised in the future that can detect persons who do not have their tissue reservoirs saturated with the vitamin. The application of such methods in the survey of patients in the clinic and in representative groups of the normal population should result in numerous interesting and valuable observations.

Vitamin B-1 and the Alimentary Canal:

Babkin (32) with his sham-feeding experiments reported interesting observations suggesting the relation of vitamin B-1 or some member of the vitamin B complex to the nervous mechanism controlling gastric secretion. During the state of vitamin deficiency there was a marked diminution in the response of the gastric glands to subcutaneous injections of histamine and the presence of food and 5% alcohol solution in the intestine. However, with the administration of yeast the responses became normal within a few days. This possibly may account for the anorexia.

Chatterjee (33), who studied the motor functions of the intestine in vitamin B-1 deficient and starved animals, found that there was a definite decrease in the amplitude, the number and intensity of intestinal contractions as well as responses to pilocarpine, atropine,

nicotine and barium chloride. This is significant as anorexia and intestinal stasis are common symptoms of vitamin B-1 deficiency. However, Molitor and Sampson concluded that vitamin B-1 has no demonstrable effect on the intestine of the normal organism (34). Its action is exerted up to the point required by the animal but not beyond.

The small and the large intestine readily absorb vitamin B-1, but in all probability efficiency of such absorption may vary individually. Theoretically, vitamin B-1 may be lost from the body in chronic diarrhea, but here the mechanism is merely a failure of absorption or an appreciable fraction of the ingested vitamin. The presence of vitamin B-1 in the feces has challenged many investigators to determine its origin. Cowgill (35) stated that any vitamin B-1 made available to the host by bacterial action within the large intestine must arise from dead and decomposed bacteria and that the variations in the amount of the vitamin found in the feces represents probably variations in the growth of the B-1 containing organisms.

Vitamin B-1 and the Heart:

Rats on a vitamin B-1 deficient diet showed bradycardia according to Birch and Harris (36). The slowing

of the heart-rate is not a characteristic feature of vitamin B-1 deficiency in dogs (35). It is true that the enlargement of the right side of the heart so characteristic of beriberi in human beings occurs with experimental vitamin B-1 deficiencies produced in different species of animals, but the physiologic response which this organ shows to lack of the vitamin is not the same in all species. Aalsmeer and Wenckebach (37) after studying the heart in a case of beriberi suggest that this organ is essentially edematous. It is certainly incorrect to designate the condition as hypertrophy as the heart can return to normal size remarkably soon with the institution of vitamin B-1 therapy. The fact that the tissue of the auricle, in contrast to the ventricle, shows marked reduction in oxygen uptake from the normal constitutes proof that these two parts of the heart respond differently to a shortage of vitamin B-1 and that the auricle is more sensitive in this respect than the ventricle. Due to this increased sensibility, the auricle becomes weaker, losed tone and suffers greater mechanical distention in the presence of the pressure exerted by the circulating blood. Therefore, one should expect that the administration of vitamin B-1 would restore the lost tone considerably, with the

result that the right side of the heart would show a prompt return to normal size. Obviously this can not be the complete explanation because much of the enlargement of the right side of the heart involves the right ventricle also.

Vitamin B-1 and the Nervous System:

Vitamin B-1 is one of the two components of the vitamin B complex which is known to be of significance in the maintenance of normal neurologic function in man. The polyneuritis of alcohol addicts (38) and the polyneuritis associated with pregnancy (39) has been demonstrated to be due to a lack of vitamin B-1 and have responded unusually well with adequate B-1 therapy. The rotational movements frequently exhibited by animals suffering from specific B-1 deficiency suggests lesions in the vestibular nuclei. Church (40) supported this view and offered evidence in this direction, reporting the discovery in the rate of perivascular hemorrhages in this region. These movements at the present time are considered secondary to more fundamental tissue changes resulting from the specific lack of vitamin B-1.

Vitamin B-1 and Metabolism:

The state of heightened metabolism, such as that produced experimentally in the administration of thyroid

and actually in pregnancy, lactation and febrile conditions, increases the organism's need for this dietary essential. Vitamin B-1 has some role in the transformation of carbohydrates in the organism and is an enzyme or catatyst necessary to carbohydrate metabolism, promoting the disposal of certain breakdown products of cell metabolism during which oxygen is taken up and carbon dioxide is given off. In studying this problem experimental animals have been allowed to subsist on vitamin B-1 deficient diets differing markedly in content of carbohydrate, protein, fat, and the time required for development of the symptoms of B-1 deficiency taken as an indication of the relation of B-1 to the metabolism of one or more of these energy-yielding foodstuffs. Diets rich in carbohydrates are more effective in producing symptoms of B-1 avitaminosis than diets rich in fats. Out of this work has come considerable discussion of the vitamin B-1-sparing action of fat. Westenbrink (41) reported that pigeons on a high carbohydrate fat-free diet developed symptoms of B-1 deficiency in nineteen days (plus or minus four days), whereas another group subsisting on a high fat carbohydrate-free diet required twenty-seven days (plus or minus seven days) for the symptoms to appear. Kemmerer

and Steenbock (42) concluded that one cannot explain the vitamin B-1-sparing action of fat on the basis of greater conservation of the store in the tissue of this dietary essential. Evans and his associates (43) offered the suggestion that the chemical nature of the fat in some way influences its action in this regard. Salmon and Goodman (44) supported this idea and found that coconut fat is the most effective natural fat of those tested. More striking yet was the observation that spastic experimental beriberi in the rat can be cured by the feeding of glyceryl caprylate or caproate.

Studies along this line seem to justify the conclusion that the function of vitamin B-1 is more likely related to carbohydrate metabolism than to fat metabolism. Westenbrink (45) has offered three possible explanations: 1. When fat is fed, the organism used in its metabolism less vitamin B-1 than it does when carbohydrate is fed. 2. Whether the diet is high in carbohydrate or fat, the vitamin is used at the same rate, but the presence of much fat in some unknown manner affects the time of onset of the polyneuritis. 3. Under the two sets of dietary conditions vitamin B-1 is used at the same rate, but when carbohydrate is metabolized a toxic metabolite arises which in the

absence of the vitamin is not removed and which, therefore, induces the polyneuritis. This last reason is obviously false.

An analysis of all the evidence at present suggests that thiamin is definitely concerned with tissue respiration, particularly as it relates to the metabolism of pyruvic acid. It demonstrates that there was justification in the early suggestions that intermediate substances arise from carbohydrate degradation, which cannot be metabolized in the absence of thiamin. Especially significant now is the early observation of Funk (46) that an increase in the carbohydrate ingestion causes a more rapid production of polyneuritis in pigeons on a thiamin-deficient ration.

Thiamin deficiency is accompanied by a progressive diminution in carbohydrate tolerance (47). The derangement of carbohydrate metabolism precedes the nervous disturbances and is manifested as hyperglycemia(48). It was shown by Roche (49) that in polyneuritis there is an accumulation in the blood of intermediate products of carbohydrate metabolism and an increase in the C:N ration in the urine. Lohmann and Schuster (50) discovered cocarboxylase is a pyrophosphate of thiamin and isolated it from yeast. This coferment increases

the in vitro oxygen uptake of brain tissue from thiamin-deficient animals. It is indicated that the vitamin does play an active role in tissue oxidations and that the hyperglycemia, loss of weight are directly attributable to a deficiency of the vitamin in the tissues.

Peters and his coworkers (51) at Oxford University have unequivocally demonstrated that thiamin is a catalyst in the oxidative removal of the lower degradation products of glucose metabolism. It was demonstrated that pyruvic acid accumulates in the blood of thiamin-deficient pigeons, and more recently Peters concludes that thiamin "..... is related specifically to pyruvate oxidase in its aerobic action." This specific action manifests itself in two ways: 1. It increases the oxygen uptake under precisely defined conditions, the so-called catatorulin effect. 2. It decreases markedly the pyruvate formed by thiamin-deficient brain tissue.

Sherman and Elvehjem (52) showed that heart and kidney tissue acts similarly to brain tissue with respect to pyruvic acid, and that the removal of pyruvate injected intravenously in polyneuritis in chicks is much slower than in normal chicks. This suggests further that in thiamin deficiency there is a failure in the tissue metabolism of pyruvic acid.

Finally, it is of importance to note that methyl glyoxal, the aldehyde of pyruvic acid, has been found in the blood and urine of beriberians and animals on a thiamin-deficient diet (53).

SURVEY OF THE CAUSES OF VITAMIN B-1 DEFICIENCY IN NON-PREGNANT AND THE PREGNANT WOMAN

Obviously, it follows that a lack of vitamin B-1, no matter what may be the cause, is responsible for vitamin B-1 deficiency. Non-pregnant women are not as likely to have this deficiency as pregnant women. However, this does not infer necessarily that therapeutic abortion will give marked relief from the symptoms and signs of B-1 deficiency or that these symptoms and signs will not follow it; but this only means that the vitamin B-1 requirements are higher in pregnancy, and if there is a deficiency more serious consequences result.

In the non-pregnant woman chronic alcoholism, diabetes, infection, hyperthyroidism, pyloric stenosis (54), diarrhea and alteration of intestinal absorption (55), cirrhosis and other diseases of the liver, arteriosclerosis, other conditions involving serious damage to vital organs, and last, but not least, deficient vitamin B-1 intake may account for avitaminosis-B-1. However, in the pregnant woman several additional factors come into the scene and thereby increase her vitamin B-1 requirements above that of the non-pregnant woman. There is a tendency in the pregnant woman, when

nauseated, to restrict her diet to concentrated carbohydrate foods which are not only low in their B-1 content but also necessitate more vitamin B-1 for their degradation and utilization. Then, too because of vomiting, the pregnant woman fails to retain all that she ingests (6). Her gestation heightens her metabolism (7) as well as increases her vitamin B-1 requirements, and it is possible that her power of assimilation is reduced (56) as there is a decrease in the gastric secretory function in pregnancy.

During the past decade it has been shown that vitamin B-1 deficiency is and has been, more or less, endemic in the United States in characteristic form(57). Not only have the modern civilized methods of food preparation eliminated a goodly portion of the vitamin B-1 which was present in similar foods in the past but also there has been a steady rise in the consumption of the highly purified foodstuff, cane sugar. No doubt this has been due in considerable measure to the great developments in the sugar industry, making the available supply greater than ever before, but the sweet taste of this product has also played a great role. That sugar is valuable as a source of energy cannot be questioned, but, to the extent that it displaces other foods

which may at the same time function as carriers of important nutrients such as minerals and vitamins, this increasing use of sugar is obviously not in the public interest. The economic status of this country has a strong influence on the situation as Dr. Hans H. Reese (58) states that forty-five million of our population have to exist at present on an annual income of $980.00 and some four and one-half million on an annual income of $98.00.

Cowgill (59) has shown that the vitamin B-1 requirements of man is directly proportional to body weight, caloric intake and metabolism. Infections, excessive exercise, etc., raising the total metabolism, not infrequently precipitate the acute symptoms of deficiency (60).

Thus, it can be said conclusively that vitamin B-1 deficiency is manifested by the fact that vitamin B-1 does not reach its proper distination in the human body where it can perform its physiologic role, whether this is due to insufficient intake, faulty absorption, or altered metabolism.

REQUIREMENTS OF THIAMIN IN PREGNANCY AND NON-PREGNANCY AND FOOD SOURCES

Owing to the apparent lack of ability of the human body in storing thiamin, and in view of its rapid loss from the tissues during short periods of deficiency, it seems that optimum nutrition, with respect to this factor, cannot be properly maintained unless the diet regularly contains this essential in adequate amounts. From the data presented in a recent review of the literature bearing on the human requirements of vitamin B-1 (59) it appears that adults require daily as a minimum approximately 300-350 international units of the vitamin which is equivalent to about 1 mg. of the pure vitamin. The latest definition of the international unit specifies that it be equal to 3 micrograms of the pure vitamin. This means that 333 international units are contained in 1 mg. of crystalline thiamin chloride. This minimum is equal to about ten international units per hundred calories daily. However, according to animal study the requirements in pregnancy are three to five times greater (61).

Sherman has estimated that if half the food calories are derived from milk, eggs, fruits, vegetables and undenatured cereal products, an ample supply of vitamin

B-1 will be provided (62). However, a study of dietary habits of large numbers of individuals, of the quantities of certain types of foods consumed, and of the high incidence of symptoms characteristic of avitaminosis-B-1, indicates that the average intake is nearer the minimum or the sub-minimum than the optimum requirement. Furthermore, Tarr and McNeile (63) report that their studies showed that the average American diet is deficient in vitamins, especially the vitamin B complex.

The presence of vitamin B-1 has been demonstrated in a wide variety of foods, but there are relatively few foods of animal and plant origin which may be considered potent sources. Therefore, in the planning of an adequate diet it is necessary to rely on several food items to supply the daily requirement.

Due to the dearth of data on the occurrence of this factor in foods and the fact that values expressed in terms of the rat growth method still comprise the major portion of the dietary calculations available, it seems unnecessary here to consider more than the general aspects of food sources of vitamin B-1 with particular reference to the precautionary measures essential to insure against unnecessary losses during manipulative

procedures, such as cooking or canning. However, it might be advantagous at this point just to mention a few good sources of vitamin B-1 and their international units of vitamin B-1 per ounce (64, 65, 66):

Almonds	24	Liver, beef	48
Asparagus, green	21	Milk, malted	50
Bacon	27	Parsnips	21
Bread, whole wheat	22	Peanuts	60
Butter	12	Peas	12
Carrots	18	Prunes, dried	21
Corn, sweet canned	15	Spinach	21
"Greens"	15	Wheat germ	203
Ham	36	Yeast	49-420

In general vegetables, including potatoes, form one of the more important groups. Exclusive of legumes, which are very good sources of vitamin B-1, they may, for all general purposes, be considered on a par with one another. Fruits may only be rated as fair, but it is important to note that they are to be eaten raw and in large quantities.

The germ portion and outer or bran layer of seeds seems to hold the concentrated vitamin B-1, and because of this legumes, nuts and whole grains are good providers. This is not so of the refined cereals and flours as the germ and bran layer are largely removed in the process of milling and refining. Pork and especially the organ meats, eggs, muscle meats are excellent sources and not subject to variation due to

changes in the vitamin B-1 content of the diet of the animals from which they come, as is the case with vitamin A.

Also it must be mentioned that milk becomes an important source of vitamin B-1 as it is ingested in large quantities and may be used without treatment, thereby, not lessening its potency.

Depending upon the conditions which prevail during the heat treatment of foods which contain vitamin B-1, the actual loss may or may not be significant. Generally, inactivation occurs gradually, as the time or temperature, or both, of heating increases. For all intents and purposes, a temperature for one hour at 100 degrees need not be considered significant. However, especially at temperatures above the boiling point, inactivation increases markedly with decreasing acidity. Losses in foods under conditions similar to those in baking have been shown recently to be as high as 50 per cent.

Vitamin B-1 is water-soluble and much of the vitamin may be lost in the process of boiling. This is not due to the boiling alone but because the water in which the food has been boiled is thrown away as it is regarded as useless. Little of the vitamin B-1 content of

foods are lost by canning, but the vitamin B-1 content of canned products is retained only if no portion of the contents is discarded.

SYMPTOMS AND SIGNS OF VITAMIN B-1 DEFICIENCY

Vitamin B-1 deficiency can be a mild or a severe disorder, depending entirely on the severity of the metabolic disturbance. Accordingly, the symptoms may vary from anorexia, numbness and tingling to severe degeneration of the nervous system with evidence of dysfunction of all systems and organs of the body. Tarr and McNeile (63) suggest that the chief early symptoms are disturbed digestive function, mild or severe, intestinal stasis, due to decreased neuromuscular control, loss of appetite, often the first of symptoms for which relief is sought, constipation and restlessness. Remissions are apt to occur when by some means or another vitamin B-1 is supplied in sufficient quantities as are also relapses when the diet again becomes deficient in vitamin B-1. The onset of vitamin B-1 deficiency is usually insidious but may be sudden and acute. The latter is probably the case in pregnancy because not only is there increased vitamin B-1 requirements but also there are vomiting and decreased gastric secretory function in pregnancy. General systemic signs appear before neurologic manifestations. Mild sensory disturbances become more continuous and severe, are worse at night and are followed by increasing

weakness, ataxia and incoordination, point involvement of position sense. Foot drop may be missed, and general paralysis of the legs seems to appear suddenly often after therapeutic abortion or delivery. Hands and arms are involved less, and weakness appears after it is well-marked in the legs. Atrophy of the distal parts may be concealed by the edema but will always be present in severe cases. The facial, glossopharyngeal, and vagus are the commonest cranial nerves effected, with corresponding aphonia, dysphagia, paresis of the facial muscles and extensive paralysis of the skeletal musculature. The syndrome closely resembles beriberi in its neuritic manifestations and heart findings. Edema and hemorrhages of the retina are not infrequent. Four cases of Berkwitz and Lufkin (2) had edema of the optic disk, three had retinal hemorrhages.

Masten (61), in a recent article, summarizes the signs and symptoms very accurately:

Skin and Mucous Membranes:

1. Atrophy, scaling, pigmentation.
2. Flattened, dry nails.
3. Dermatitis.
4. Ulceration.
5. Redness of mucous membranes.
6. Gingivitis.
7. Edema.

Alimentary Tract:

1. Anorexia.
2. Glossitis.
3. Stomatitis.
4. Proctitis.
5. Vomiting.
6. Diarrhea.
7. Constipation.
8. Hypochlorhydria.
9. Achlorhydria.
10. Atony.
11. Ulceration.
12. Loss of weight.

Cardiovascular System:

1. Tachycardia.
2. Bradycardia.
3. Cardiac enlargement.
4. Hypertension.
5. Normal blood pressure
6. Hypotension.
7. Changes in the E.K.G.
8. Reflex irritability (vagus).
9. Pulmonary congestion.
10. Pneumonia common.

Hemopoietic Organs:

1. Hypochromic and hyperchromic anemia.

Nervous System:

1. Sensory
   a. Paresthesia
   b. Numbness
   c. Pains worse at night
   d. Present in legs before arms
   e. Fleeting at first, later persistent
   f. Position and vibratory sense disturbed

2. Motor
   a. Weakness at first
   b. Paralysis may be gradual, first in legs
   c. May come on suddenly, beginning with foot drop.

3. Cranial nerves
   a. May not be involved
   b. Nystagmus common
   c. Severe cases: bilateral facial paralysis, vocal cord paralysis, dysphagia
   d. Hemorrhages of the fundus and edema of the optic disk

4. Mental
   a. Loss of memory, especially for recent events
   b. Emotional instability
   c. Anxiety, restlessness, confabulation
   d. Delerium in severe cases

It is difficult to explain all the above enumerated symptoms as no clear and accurate explanation has been offered to date. However, the cardinal symptoms: degeneration of the nervous system, cardiac enlargement and dysfunction, edema, gastrointestinal disturbances, muscle atrophy, and anorexia can be explained theoretically if not logically.

Pathologically, the outstanding effect in the nervous system is that of disintegration of the myelin sheaths of the peripheral nerves and vacuolation and liquefaction necrosis of the ganglion cells of the mesencephalon, metencephalon and anterior horn cells of the spinal cord. Whether the neuritic symptoms are directly attributable to these lesions or functional interference owing to the accumulation of metabolic products, particularly pyruvic acid and perhaps lactic acid, is not clear even today. Moreover, Davison and Stone (67) have shown that inanition alone may cause marked change in the peripheral nerves. Wolbach (68) concludes that these changes should be explained on the basis of secondary effects rather than primary

pathological effects of thiamin deficiency.

Cardiac enlargement was ascribed by Aalsmeer and Wenckebach (69) as due to edema. Then Newcomb (70), unable to note any significant difference in the water content of cardiac muscle from cases of human beriberi and pigeon polyneuritis concluded that the cardiac enlargement was a case of true hypertrophy. Recently, Wenckebach (71) described the beriberi heart as an enlarged heart with rapid rate and a throbbing systolic impulse, large bounding pulsations in the peripheral arteries, venous engorgement, warm extremities and edema. Weiss and Wilkins (72) showed that the E.K.G. in such cases are abnormal, being characterized by changes in the T waves, low amplitude, and prolongation of the electrical systole (Q-T). Birch and Mapson (73) contend that the observed bradycardia is due to a failure in the deaminase mechanism which results in increased accumulation of adenylic acid in the tissue. Relationship between the cardiac changes and the blood is indicated, since there is a tendency toward possible increased lactic acid. There is a suggestion of a failure in the metabolism of carbohydrates in these blood changes and in view of this it is easy to conclude that the heart does not function normally owing to the interfer-

ence with carbohydrate metabolism in that organ.

Probably other dietary deficiencies other than thiamin are related to the condition of edema, and in all probability protein insufficiency is of considerable inportance.

Cowgill (64) points out that in locations in which beriberi is endemic conditions such as amebic dysentery may constitute the precipitating cause of the deficiency disease. In experimental thiamin deficiency he further noted that there was a lack of tone of the gastric musculature and that this is accompanied by a gastric hypochlorhydria. Sparks and Collins (74), after repeating the experiments of Hargreaves, Fletcher, and Dickson (75) concluded that vitamin B-1 deficiency in rats causes a marked increase in the volume of the colon.

Only presumptive evidence concerns thiamin deficiency in human gastrointestinal dysfunctions. However, Vorhaus, Williams, and Waterman (76) noted beneficial results when 8 cases of gastrointestinal hypotonia were treated with 10 mg. daily doses of thiamin by mouth, and Strauss (56) concluded that there is definite decreased gastric secretory function in thiamin deficiency in pregnancy.

Muscular atrophy is a prominent, non-specific symptom of vitamin B-1 deficiency, but it need scarcely be mentioned as anorexia and resultant inanition are marked. It may be assumed that the fall of body weight and muscular wastings are attributable to these factors.

Loss of appetite is one of the sirst symptoms of vitamin B-1 deficiency, but it occurs also in other deficiencies and in a much less degree, however. In fact we do not know of any deficiency which occasions such a marked degree of anorexia as that caused by vitamin B-1 deficiency. Some suggestion of the general relationship between thiamin and appetite is indicated by the significant correspondence between the caloric needs of the body and desire for food. Owing to the failure of carbohydrate metabolism in vitamin B-1 deficiency, the appetite is lessened as it appears that the appetite for food is influenced in some manner by the blood level of the intermediate products of carbohydrate metabolism.

PATHOLOGY OF VITAMIN B-1 DEFICIENCY

Only the severe forms of vitamin B-1 deficiency can be considered pathologically as they are the only ones which come to autopsy to be examined. The mild forms clear up with adequate vitamin B-1 therapy. Berkwitz and Lufkin (2) made the interesting statement, which has its corollary in observations made long ago in beriberi, that the microscopic findings in the nervous system are less conspicuous than the severity of the clinical symptoms. It may be mentioned that the findings in vitamin B-1 deficiency of pregnancy are very similar and probably identical with beriberi. However, there are not many cases reported in the literature on which post-mortem examinations have been performed. Therefore, it is important that these reports be reviewed in regard to the respective findings.

Schaupp (77) reports a case which was examined after therapeutic abortion had been performed. Grossly, the vessels over the cortex were markedly congested with occasional small petechial hemorrhages over the cortex; there was moderate pulmonary edema; the kidneys showed on cut section cloudy swelling with occasional hemorrhages into the pelves; and the liver was small. Microscopically, the kidney showed cloudy swelling and

especially in the convoluted tubules; the liver showed little cloudy swelling and fatty degeneration and necrosis of central lobular cells; the lungs were edematous, infiltrated with leucocytes in patches, bronchioles were filled with purulent material, and the lung otherwise was normal in appearance; the meningeal vessels of the brain were moderately congested, leucocytes were prominent among the red blood cells, small hemorrhages were scattered throughout the cortex with slight central necrosis.

Ford (78) in 1935 reported hemorrhagic bronchopneumonia in the lower left lobe of the left lung, massive congestion of the lungs, subpleural hemorrhages, subpericardial hemorrhages, cloudy swelling of the myocardium, cloudy swelling of the liver with considerable inflammatory infiltration of the portal system, edema of the spleen, edema, congestion and cloudy swelling of the kidneys with few small foci of subacute inflammation and dilatation of both pelves, few petechiae in the bladder mucosa, no brain abnormality and degeneration of some anterior horn cells in the spinal cord, particulary in the lumbar region.

Theobald (79) in 1936 reported degenerative changes in the peripheral nerves, anterior horn cells, and

petechial hemorrhages in the brain and cord as did also Berkwitz and Lufkin (2), Luikhart (7), and Ford (78).

Berkwitz and Lufkin (2) on three autopsied cases reported no gross anatomical changes, but microscopically there were degenerative changes in the peripheral nerves and anterior horn cells, more marked in the lumbar region, increased loss of nissl substance, swelling of cells, eccentricity of nuclei, and occasional cell necrosis. There were also petechial hemorrhages in the brain and spinal cord, and the liver and kidney showed mild cloudy swelling.

DIFFERENTIAL DIAGNOSIS

Vitamin B-1 deficiency in pregnancy, if present, makes itself very obvious, and the diagnosis is not made with difficulty. Usually a brief inquiry into the history with special regard as to diet, vomiting and other gastrointestinal disturbances and the alleviation of the symptoms by the therapeutic use of thiamin will cinch the diagnosis.

The differential diagnosis may present an altogether different picture as other forms of polyneuritis may perplex the problem. As a rule in lead poisoning only the motor nerves and the anterior horn cells of the spinal cord are affected. Pain is rare and involvement of sensation is minimal. The upper extremity is more often affected with first a weakness of the hand, then a wrist drop in a few days, foot drop occuring later. A history of colic, the appearance of a characteristic lead line and the stippling of the red blood cells further aid in establishing the diagnosis. The heavy metals closely resemble the action of lead in their toxic action.

The occasional contaminant of jamaica ginger, triorthocresyl, apiol and other abortifacients act like the heavy metals in that the involvement is essentially

motor in type. The paralysis develops in a few days after the abrupt onset and usually first affects the nerves of the legs, many patients presenting foot drop alone. Advanced cases present involvement of the arms and hands. Disturbance of sensation is minimal and pain in the calves without much tenderness is a common but transient symptom at the onset.

Affection of the proximal rather than the distal portions of the limbs occurs commonly in infectious polyneuritis. The characteristic picture is involvement of the shoulder girdle and the upper thighs, cranial nerves, especially the seventh, and the spread of weakness is peripheral instead of proximal. The protein content of the spinal fluid may be increased.

In diptheria an ascending perineural lymphogenous intoxication commencing with the side of the infection is the usual picture. Thus, the first sign in faucial diphtheria is palatal paralysis, in laryngeal diphtheria, laryngeal paralysis. Later it spreads to contiguous centers in the nervous system. The sacral nerves may be involved when the lesion is on the buttocks as in diptheritic saddle sores.

Arsenical polyneuritis simulates beriberi most closely, but this condition occurs after acute poisoning rather than chronic intoxication, therefore, the history is very significant. Burning, pain and paresthesia are most pronounced and motor changes are less marked than sensory changes.

The differentiation from acute poliomyelitis must be emphasized and rests on the incidence of the condition in association with epidemics and on slight increases in white cells, globulin and sugar in the spinal fluid, together with early rises in the colloidal gold curve in that condition (80).

VITAMIN B-1 USED THERAPEUTICALLY

Substances rich in vitamin B-1 or the pure crystalline vitamin B-1 may be employed therapeutically. However, it is wise to use both methods. 20-50 mg. daily of the pure vitamin B-1 should be injected intravenously in the definitely diagnosed case of vitamin B-1 deficiency. This amount is probably in excess to the amount required, but it is best to over-treat than to under-treat as no ill-affects are liable to occur with a massive amount. 100 mg. has been administered intravenously without harmful affect. After a fortnight of intravenous therapy oral administration can be used in the same dosage, or, if the injections are continued, the dosage is decreased to 10 mg. daily until the patient is completely relieved of all symptoms.

Plain or autolyzed brewers' yeast serves as a convenient means of administering the other portions of the vitamin B complex. Thirty grams of brewers' yeast of a good potency given three times a day is generally sufficient for the treatment of the less seriously ill patients, particularly if there is no reason to suspect the presence of gastrointestinal disturbances which might interfere with the absorption of the vitamin if given orally. It is very important to start vitamin B-1

therapy immediately upon diagnosis because vasomotor collapse can appear without warning in patients with beriberi heart.

Deficiency disease in man, unlike that produced experimentally in the animal, is seldom due to a deficiency in one single factor. Therefore, a diet low in vitamin B-1 stands a good chance to be low in other portions of the vitamin B complex as well as vitamin A and C, iron and the other minerals. Glossitis, anemia and pellagra frequently accompany vitamin B-1 deficiency and it is wise, therefore, to supply adequate amounts of vitamin A and C, iron and foods rich in the other portions of the vitamin B complex. The glossitis and skin manifestations have been controlled beautifully with dilute intramuscular injections of liver extract in doses of 10-20 cc. or more daily (81).

The polyneuritic and cardiovascular manifestations of vitamin B-1 deficiency have been very satisfactorily treated with the administration of vitamin B-1. An almost complete remission of the signs and symptoms in a not far advanced case of polyneuritis may disappear in the matter of a few weeks. However, the more advanced the case the more degenerated are the nerves and the longer the period of time correspondingly that

will be required before complete recovery occurs. A viable nerve cell in the spinal cord or posterior ganglion is necessary before the peripheral nerves will regenerate. This regeneration commences at the cell body at the rate of 1 mm. per day, therefore, it requires a long time. Treatment must continue unremittently. Naturally it follows that regeneration of completely degenerated cells and axis cylinders within the central nervous system and complete recovery of functions lost resulting from cerebral or posterior column degeneration cannot be expected, even though marked improvement in these functions occurs not infrequently.

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