The Role of Thiamine in Research with Animals and in Humans

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Thiamine, also known as aneurin, is a water-soluble vitamin which is stored for a limited period in the body. Human experiments seem to indicate that a storage over a period of four to 27 days is the usual case; after that time period a deficiency sets in. However, thyrotoxic patients are unable to store vitamin B-1. Pigs store thiamine in the muscle tissue. After 35 days of thiamine supplement a maximum storage has occurred in pigs (Robinson, 1966).

Thiamine is found in enriched white bread and enriched corn flakes. A trace of thiamine is also found in cottage cheese, oranges, raw potatoes, white eggs, and nuts. Brewer's yeast and wheat germ contain the most of this vitamin (Williams, 1971).

The effects of the growing season, temperature, and location of growth in the thiamine content of plants vary with the species. Light stimulates the synthesis of thiamine. With maturation thiamine increases in oats, wheat, potatoes, and peas.

Thiamine is stable during the storage of cereal grains of proper moisture content. There appears also little loss of thiamine during frozen storage of fish and vegetables. But thiamine oxidizes when exposed to air and when cooked. The milling of cereal grains removes a large proportion of the thiamine (85 percent).

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TABLET

Thiamine Average value of meg per 100 gm

Dried beans and peas	680 mcg
Nuts	560 mcg
Whole grain cereal	370 mcg
Liver, heart, kidney, brain	100 mcg
Flour	70 mcg
Root vegetable	60 mcg
Spinach vegetable	1600 mcg
Milk	40 mcg
Fruits	30 mcg
Pork muscle	600-800 mcg
Common fish	50-90 mcg
Hen eggs	170 mcg
Egg yolk only	500 mcg
Dried brewer's yeast	1820 mcg
Wheat germ	2050 mcg

Roasting of beef involves a thiamine loss of 36-53 percent. The daily required amount of thiamine is 1.5 mg, but research indicates that individual differences as to the body's digestion of thiamine has been noticed. Under normal circumstances the need for thiamine may vary from 0.5 mg to 1.5 mg/1,000 cal. This is the recommendation of the National Research Council. It is very likely that individuals according to their

genetic make-up require different amounts, and R. Williams coined the term genetotrophic diseases for diseases that are caused by a genetically larger requirement of a nutrient.

Authors seem to agree that a thiamine deficiency is not synonymous with beriberi disease. Piatt (1967) considers subacute thiamine deficiencies related to protein and calorie deficiency. Thus lack of protein intake may lead to a thiamine deficiency. The presence of thiamine is necessary for the oxidation of carbohydrates in the brain. Some workers have found a connection between thiamine and fat metabolism. Less thiamine is needed for the fat metabolism. Fat in the diet conserves thiamine presence in the tissue (Westenbrink, 1933). But others have not been able to confirm these findings (Robinson, p. 52, 1966). Holt and Snyder-man reported in 1955 that 18-month-old infants excrete less thiamine in the urine if fed a high-carbohydrate and low-fat diet. However, if fat was substituted for carbohydrate, a considerable spill of thiamine was found in the urine (infant requirement 0.4 mg thiamine/kg). Thus more thiamine is needed for metabolic purposes if a high-carbohydrate diet is given. A range between 0.17 and 0.23 mg/1,000 cal. appears to protect against thiamine deficiency. But young adult men need more: 0.33 mg/1,000 cal.

Light and Cracas demonstrated in 1938 that different strains of white rats have inherently different levels of need for thiamine. One strain responded with less growth at the 4 mcg level per day, and another strain only responded with a similar lack of growth when 2 mcg per day were administered. They still showed good growth at 2 mcg a day. As to human individual needs, Najjar and Holt (1943) conducted a study with nine boys, age range 16-23, using 1 mg per day with a slow and gradual reduction. The idea was to find out at what stage of below minimum *B-1* intake symptoms such as anorexia, vomiting, or edema would set in. Even at the 0.1 mg daily intake no symptoms were observed.

However when thiamine was eliminated completely four out of nine developed clinical thiamine deficiencies, one was borderline, and the other four showed no signs of deficiencies during seven weeks of observation. The analysis of feces of the eight individuals showed that those who exhibited no symptoms had about 20 times as much thiamine excretion in the feces as those who showed symptoms. The assumption that absence of clinical deficiency is equivalent to an absence of thiamine needs seems to be incorrect (Williams, 1973).

In another study by Dick et al. reported in 1958, thiamine-deficient diet was given to eight teen-aged boys for a short period of time. It was found that one of the eight boys always had a higher excretion of thiamine in the urine as compared to the others, although he was under the same controlled thiamine-deficient diet.

In an experiment with healthy men who were maintained for several months under strictly controlled diet conditions, it was observed that one normal person may excrete two to three times as much thiamine as another person (Mickelsen et al., 1947).

Another study found that children on an ordinary diet excrete 10-14 percent of their intake of thiamine, but after 0.5-1.0 mg by mouth daily the output in different individuals varied from 0-41 percent, but the average was still only 14 percent. Thus these studies seem to prove the individual differences as to needs for thiamine.

Oldham et al. (1946) report that young women on a diet containing varying levels of thiamine dropped to a blood level from 5.2 to 3.8 mcg/100 ml after 59 days on an average intake of 295 mcg/24 hours. Subjective symptoms were prevalent, which suggested a subclinical deficiency.

An adult human body does not retain more than 30 mg thiamine. The body continuously loses thiamine in the urine, feces, and perspiration. Thiamine in the form of thiamine triphosphate has been found in the-liver, kidney, and brain of rats, and in the heart, spleen, lung, adrenals, and muscles in man. Red blood cells contain more thiamine than leukocytes. The thiamine concentration in milk varies with the species.

Cowgill (1934) studying the requirements of thiamine in mice, rats, pigeons, dogs, and

human beings found that their requirement is proportional to their weight. Dann (1945) found that protein and alcohol have a thiamine-sparing action, that is, the thiamine requirement may be down to zero. The thiamine-sparing action is probably caused by the reduction of carbohydrates in the diet. Thiamine is probably not involved in the enzyme system necessary for the metabolism of fats (Sebrell, 1972). Penicillin also has a thiamine-sparing action. Penicillin increases the available thiamine by the intestinal micro-flora. During lactation, rats need five times more thiamine, and thiamine requirements for rats in old age increase greatly (Mills, 1946). Also lowering of the environmental temperature increases the thiamine requirements of rats (Hegsted and McPhee, 1950). Mills (1943) found that at a high environmental temperature of 91 °F rats require twice as much thiamine.

Ershoff (1950) demonstrated that rats could survive on a thiamine-deficient diet for an average 64 days at 74°F (23°C), whereas on the same diet the average surviving time was only 27 days at 36°F (2°C). Thus vitamin B-1 deficiency reduced the survival time of rats if exposed to cold temperature, and the extremes of temperature increased a need for thiamine! It is thought that several B vitamins are synthesized by microorganisms in the gut, some of them to such an extent that this may replace the intake of food. This may also be true for thiamine, however only for a limited time period.

Overdosage of thiamine may produce in humans hyperthyroidism, tremors, tachycardia, and sweating. But generally it has no toxic effects if given in moderate doses. The lethal doses of thiamine by various routes of administration have been determined in a number of species (Williams, 1938). An intravenous injection in mice of 125 mg/kg, in rats 250 mg /kg, dogs 350 mg/kg, rabbits 300 mg/kg, and in monkeys only 600 mg/kg caused the first toxic symptoms (Perla, 1937).

However, intravenous injection of 50 mg/kg daily for a period of four weeks in rabbits failed to show loss in weight or other toxic manifestations (Perla, 1939).

These data and the absence of evidence of cumulative toxicity give evidence for the very large margin of thiamine.

No toxic effects of thiamine administered by mouth have been reported in man. However, symptoms of overdoses have been reported (Mills, 1941), such as hyperthyroidism, e.g., nervousness, tremors, tachycardia, and sweating. In the rare instance in which parental administration is resorted to, the reaction of anaphylaxis, cyanosis, and hemorrhage into the gastrointestinal tract must be kept in mind. But injections by the subcutaneous, intramuscular, intraspinal, or intravenous routes in doses 100 times larger than the daily doses (10 mg) have been well tolerated.

Some authors suggest that B-1 deficiency together with an abnormal high level of estrogen may lead to a precancerous state (Robinson, p. 63, 1966). But Sebrell (p. 117, 1972) reports in a group of normal and cancer tissue studied that the cancer tissue had 71 percent more of thiamine level than the normal tissue.

Let me describe the symptoms of beriberi first, then the description of a subclinical thiamine deficiency will follow. At the onset the beriberi patient may suffer from a bout of fever, increased pulse rate, and increased pyruvic acid in the blood stream. Clinically a degeneration of the nervous system is noticeable as indicated by a loss of ankle jerks, exaggeration of knee jerks, and a fullness or tightening of the calf muscles associated with pain. The patient experiences pain when walking. Muscle cramps occur, especially at night. The nerve degeneration is similar to those caused by poisoning from alcohol, lead, or arsenic. The beriberi heart disease is the only heart disease attributable to a deficiency of a single nutrient. It is in general curable.

In North America and Europe these types of heart problems are common in the chronic alcoholic patient. Usually 100 mg thiamine are given. The most characteristic features are ataxia (coordination problems), amblyopia (dimness of sight), and burning feet. Adults suffering from deficiency show psychological symptoms of anxiety, depression, irritability, and increased sensitivity to noise and pain. Paralysis and death

follow in severe cases. Alcoholic polyneuritis is a B1 deficiency due to chronic alcoholism. The high intake of calories in the form of alcohol increases the B-1 requirements. Gastrointestinal disturbances which occur often lead also to defective absorption of B-1 in the form of food.

A controversial report states that alcoholic neuritis is not due to the neurotoxic effect of alcohol. In an experiment 10 alcoholics continued to drink whiskey while they were supplied by *B-1* concentrates. Improvement occurred in all patients. Deficiency of B-1 causes changes in the cortical electrical activity. Vomiting and nervousness as seen in the alcoholic are associated with those EEG changes. Acute B-1 deficiency gives rise to the clinical picture of Wernicke's encephalopathy in which hemorrhages occur in the upper midbrain and diencephalon. Clouding of consciousness of various degrees is present. In the milder cases the EEG shows a general slowing of the alpha rhythm, giving place to a theta dominant record. In more advanced cases the EEG shows generalized delta waves, bilateral and symmetrical. There is a correlation between the clinical state and the EEG abnormalities.

In many parts of the world poorly nourished women produce healthy babies and seem to nurse them adequately; however, more still birth and low birth weight have been found in undernourished women. Infantile beriberi, cretinism and deafness, and mutism due to deficiencies of thiamine and iodine in the maternal diet have been found in newborn infants. The highest incidence is usually found between the second and fourth months of life. The infant shows aphonia, or a characteristic cry, and cardiac failure. Improvement is rapid after 10-50 mg thiamine hydrochloride i.m., but neurological recovery is slow. Polyneuritis during pregnancy may arise through increased metabolic requirements of the fetus, and the lack of thiamine may be aggravated by loss of food in vomit (Robinson, 1966).

Now let's discuss the subacute effects of thiamine deficiencies:

It is well known that the normal urge to eat is related to a sufficient supply of thiamine. It may well be that the often-diagnosed neurosis of anorexia nervosa may be related to a subacute thiamine deficiency, since extreme lack of appetite and vomiting are the clinical symptoms. In an experiment reported by Miller et al. (1955), four-day-old pigs were fed a thiamine-deficient diet. After 12 days loss of appetite (anorexia), vomiting and loss of weight were observed, and four weeks later the animals died. Those animals that received 0.5 mg thiamine per kg showed the same symptoms leading to death, only this death occurred later. All deficient pigs revealed congestion of the heart and liver. Thus the pigs showed the earlier mentioned beriberi heart disease. Two prominent symptoms of thiamine deficiency are anorexia and weight loss, or growth failure in young animals. While all or most nutritional deficiencies result in appetite loss, thiamine deficiency causes a more abrupt loss. Also thiamine promotes the recovery of appetite in a more prompt way than does any other known nutrient.

It has been shown that thiamine deficiency impairs the absorption of glucose and results in gastrointestinal symptoms such as hypotoxicity, sluggish mobility, increased gastric emptying time, and gastric ulcers.

Anorexia in rats has been found to be related to thiamine deficiency. Rats treated with oxythiamine (a thiamine antagonist) suffer under local lesion in the gut—OTH does not penetrate the blood-brain barrier in significant amounts, nor does it produce any observable neurological disturbance. Treatment with (PTH) pyrithiamine (a thiamine antagonist) of thiamine-deficient rats causes anorexia after 12 days and after ataxia has occurred. It was found that the enzyme transketolase (KT) activity is markedly decreased by a deficiency of the coenzyme thiamine diphosphate; this is more so than that of pyruvate dehydrogenase (PyDH). The decrease in transketolase (TK) correlates closely with anorexia symptoms and with malabsorption, or nonutilization of food. More studies are needed to clearly define the role of transketolase activity in the development of the

characteristic disturbances in appetite.

Infections may also affect thiamine metabolism. Severe infections may lower the thiamine pyrophosphate, a coenzyme, by as much as 50 percent. This has been observed in patients who have been febrile and anorexic for one week (Gilbert et al., 1969). Riddle (1945) has found that the respiratory infections by streptococcus haemolyticus in mice increased the resistance when B-1 was administered.

As to animal studies, it has been found that the learning abilities of rats deteriorate if the thiamine intake is reduced to 3 mcg; 12.5 mcg is the recommended daily dosage for rats. If rats were fed 100 mcg per day, they performed above average in their maze-learning abilities (O'Neill, 1949). Thiamine deficiency resulted also in a marked deterioration of the work performance of swimming rats, which was resolved by administration of thiamine. Vitamin B-1 deficiency also reduced the survival time of rats exposed to cold. Rats kept at 5°C ate about 10 g of food per day more than rats kept at 25°C (Robinson, p. 50, 1966). When young rats were developing acute deficiency symptoms and then were cured by small amounts of thiamine, and when this experiment was repeated several times, the animals showed at autopsy enlarged hearts due to dilation of the right auricle, necrosis of the muscle fibers, and pathological changes in the pulmonary veins (Robinson, p. 51,1966). Thus a lasting defect remains even after the observable cure.

In another experiment reported by Lih and Baumann (1951), it was found that growth of newborn rats is inhibited if they are put on a thiamine-deficient diet. If placed for one month on 1 mg B-1 daily supplement, after a four-week deficient diet, the rats would gain weight rapidly. If the amount of B-1 was doubled to 2 mg thiamine per kg weight, the weight gain increased to 45 percent as compared to the 1 mg B-1.

Thus the general growth has to do with the amount of thiamine intake. Of course thiamine is only one of the links in the nutritional chain. In rat experiments the heart rate of vitamin B-1 - deficient rats was found to be considerably lower than before the animal was fed a thiamine-deficient diet. The heart beat was measured by an electrocardiograph and again 24 hours after a single dose of thiamine was given to the animal.

Pigeons and rats also develop convulsions if vitamin B-1-free diet is given and recover when thiamine is added to the diet (Robinson, p. 30, 1966). It was also found that the blood sugar of chicks is reduced during the first 10-14 days on a thiamine-deficient diet; it then increases, and when convulsions occur the blood sugar may have twice the normal value. Injections of thiamine restore the blood sugar level to normal.

An interesting report from China (Zing Yang Kuo, 1960) indicates that aggressive behavior in Japanese grey quails was stimulated and increased if thiamine intake was increased, while with a thiamine-deficient diet the birds became fatigued and depressed and refused to fight or defend themselves when attacked.

In China these birds are used for fighting and gambling. The baseline of the fighting habits of 30 birds was recorded, and then they were fed 1 mg thiamine for one week. Two-thirds of the Japanese grey quail upgraded their fighting habits after two or three days of intake of thiamine. After withdrawal of thiamine, 43.3 percent retained their fighting habits for another 22 days before they re-established their previous fighting habits. This means that the blood level of thiamine remained high. The author points out that habituation to fighting had been found to be also an important factor, but the influence of thiamine was also significant. On the other hand a downgrading of fighting habits was found in 83 percent of 30 birds when fed a thiamine-deficient diet. One week after the diet started the birds increased weight and became inactive, paying little attention to other birds. When attacked they did not defend themselves, but jumped out of the pen or accepted the attack passively and submissively. Although animal studies cannot be generalized for humans, it may be worthwhile considering thiamine as an antidepressive agent.

Josef Brozek and H. Guetzkow (1957) report the following investigation. Ten young clinically healthy and normal men were fed a thiamine-deficient diet. For 15 to 27 days the thiamine intake was decreased to 0.015 mg per 1,000 cal., or 0.050 mg per day. The subjects received otherwise a well-balanced diet and a supplement of riboflavin, nicotinamide, pyridoxine, vitamins A, D, and C, calcium pantothenate, autoclaved yeast, and choline hydrochloride. The subjects walked daily outdoors and did additional exercises.

Before the experimental period of thiamine deprivation the subjects were divided into three groups, each receiving a supplement of thiamine. Four subjects received 0.6 mg, four subjects received 1.01 mg, and two received 1.81 mg per day during the standardization period of one-month duration. Thus two groups were fed a thiamine intake below the recommendation by the National Research Council's recommendation of 1.5 mg per day.

The appearance of subjective and objective symptoms varied according to the period of partial restriction. Those previously receiving the highest thiamine intake remained without symptoms up to 27 days.

The first signs of deficiency were anorexia and nausea (at the fifth day in the lowest thiamine group). Another worker reports that edema was the early symptom in experimental human thiamine deficiency (Elsom, 1940).

The neuropsychiatry examination revealed: weakness, paresthesia (sensation of skin), muscle tenderness, peripheral nerve involvement, headache, feeling of being cold, poor eye-hand coordination, lowering of pressure-pain threshold, and deterioration of manual speed and toe-reaction time and manual steadiness.

A general debilitation and personality disturbances were found. When this critical level was reached the subjects were fed supplements of thiamine to bring them back to their normal functions.

On a self-rating neurasthenia scale, all subjects showed marked deteriorations in the area of:
Concentration
Headaches
Getting impatient
Inability to sleep at night
Lack of mental alertness
Lack of ambition
Fatigue
Nervousness
Numbness
Irritability
Burning sensations
Forgetfulness, loss of memory
Dizziness, etc. On the Minnesota Multiphasic Personality Inventory (MMPI), psychoneurotic syndromes such as hypochondriasis, depression, hysteria, and anxiety were found on a significant level ($p < 1$).

This study seems to indicate that so-called psychoneurotic symptoms or psychosomatic symptoms such as anorexia, depression, fatigue, numbness, and headaches are related to thiamine subacute deficiency if the careful dietary history (including alcohol consumption) provides such indications.

Horwitt et al. (1946) report on a study in which psychiatric subjects (ages 24-42) were given a supplement of 6 mg thiamine per day, which then was reduced to 200 mcg daily. In a few months the subjects manifested exaggerations of their psychotic complaints, showed distinct changes in attitude towards their environment, a gradual restriction of activity, a dulling of interest and ambition, and a diminished desire to please. The description of these symptoms also indicates that psychiatric symptoms of depression seem to be related to B1 subacute deficiency.

Information with respect to thiamine and mental disease is incomplete. Thiamine deficiency involves malnutrition of cells in the hypothalamus and basal ganglia. Glial cells and neurons show eosinophilia of the cytoplasm with some condensation of the nuclear chromatin, suggesting leukocyte infiltration which is more marked in larger and more advanced lesions (Victor et al., 1971).

Also in regard to the role of thiamine deficiency in alcoholics, the reports are contradictory. While some authors relate

hallucinations of the alcoholics due to lack of thiamine, other authors found that thiamine deficiencies are not clearly related to visual or auditory hallucinations (Blackstocketal., 1972).

More studies are needed to give us more information on the nutritional and clinical values of vitamin B-1.

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