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Thiamine deficiency

and its prevention and control in major emergencies

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Thiamine Deficiency

A clinical syndrome that arises insidiously as a result of a severe, prolonged deficiency of thiamine in the diet, manifested in the initial stages by anorexia, malaise, and weakness of the legs, frequently with paraesthesia; there may be slight oedema and palpitations. The disorder may persist in this chronic state or may at any time progress to an acute condition characterized either by cardiac involvement with oedema or by peripheral neuropathy; forms intermediate between these two extremes may also occur. It is thought that the basic cause is the inhibition of a series of enzyme-catalysed cleavages of carbon-carbon bonds in which thiamine diphosphate is a coenzyme.

Synonyms: beriberi; Ceylon sickness; occidental beriberi (in part); oriental beriberi (in part); rice disease.

Note: The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi), but may also arise if highly refined wheat flour forms a major part of the diet, in alcholics, and in food faddists (occidental beriberi). Owing to the confusion that has surrounded the use of 'beriberi' terms, it is recommended that they be abandoned.

Source: International Nomenclature of Diseases. Vol. IV Metabolic, Nutritional, and Endocrine Disorders. WHO, Geneva 1991 pg 277.

Introduction

Scope

This is a document on thiamine deficiency, which looks at the risk factors leading to outbreaks of thiamine deficiency, describes the signs and symptoms of the deficiency disease, and discusses the strategies to prevent the deficiency in populations affected by major emergencies. A literature review of the epidemiology of thiamine deficiency, the properties and functions of the vitamin thiamine, and a discussion of food sources of this vitamin and its stability is also provided.

Background

Outbreaks of the micronutrient deficiency disease 'beriberi' have occurred frequently in refugee and displaced populations dependent on international food aid. Nutritional deficiencies do not generally occur with the consumption of a moderately varied diet. However, the food rations distributed are usually not balanced in energy, protein and micronutrient content. Moreover in the initial phase of an emergency the affected populations are usually survivors of varying periods of minimal food intake and many are ill with infections. Thiamine deficiency occurs where the diet consists mainly of milled white cereals, including polished rice, and wheat flour, all very poor sources of thiamine. Thiamine deficiency can develop within 2-3 months of a deficient intake and can cause disability and death. Thiamine deficiency in refugees has been seen in Thailand at the beginning of the 1980's and in the 1990's, in Guinea (1990), Djibouti (1993) and in Nepal (1993-1995).

Recent outbreaks of thiamine deficiency

In the general population

In the northern and north eastern parts of Thailand, thiamine deficiency, confirmed biochemically, was reported to be common in spite of adequate but marginal thiamine intakes, with the daily food consumption of the people being large amounts of glutinous rice, raw fermented fish and vegetables. Betel nut chewing was found to be common. From the data presented by Vimokesant and others (1982), anti-thiamine factors in the diet may have been a precipitating factor causing the thiamine deficiency in these population groups.

Thiamine deficiency has been observed in pregnant women who have increased demands for thiamine. Rolfe and colleagues (1993) reported that it may be an unrecognized complication of pregnancy in urban areas in certain parts of Africa and Asia and be a cause of preventable maternal death. The potential for large outbreaks of thiamine deficiency exist in urban areas in West Africa where polished rice is the staple diet with many asymptomatic people probably having subnormal thiamine levels. In 1988, an outbreak of thiamine deficiency occurred in a rural area in The Gambia. At least 140 people, mainly young men, were affected and 22 died (Tang et al, 1989). In 1990–1991 38 patients with thiamine deficiency were seen in a hospital in The Gambia and 4 patients (10.5%) died (Rolfe et al, 1993). In areas where rice is the staple, cases have been reported each year in the rainy season when food supplies are lowest and there is intense agricultural activity with increased energy expenditure. There have also been reports of outbreaks in confined populations in The Gambia: in prisons, psychiatric units, among communally-fed policemen, as well as amongst migrant workers in Ethiopia (Marsden et al, 1967; Rolfe et al, 1993).

In Europe, North America and Australia, thiamine deficiency is common among alcoholics and usually manifests itself as the Wernicke-Korsakoff syndrome but has also been reported in patients on restricted diets for obesity, those who receive total parenteral nutrition and in those who are on fad diets or whose intakes are high in carbohydrate and low in thiamine (Kawai et al, 1980; Anderson et al, 1985; Feldman, 1988). Little attention has been given to possible thiamine deficiency in infancy. Studies in Australia have revealed quite unexpected incidence of biochemical thiamine deficiency in pregnant mothers at term and in apparently healthy infants subsequent to the neonatal period. Thiamine deficiency was found in infants and their mothers coming from families who had a high incidence of Sudden Infant Death Syndrome (Australian Health and Medical Research Council, 1978; Wood et al, 1980; Jeffrey et al, 1985).

In active young adults, subclinical yet biochemical thiamine deficiency may be a cardiovascular and a psychological stress factor as seen both in Japan (Anderson et al,1985) and the USA (Lonsdale et al,1980). Symptoms reported in the patients in the USA were those of neurotic dysfunction that are frequently treated by sedatives and psychological counselling. Diet history revealed increased consumption of high carbohydrate foods such as sweetened drinks and products made from refined wheat flour for long periods of time. The symptoms in the patients improved following the administration of thiamine.

Thiamine deficiency occurs sporadically in people who are socially isolated, suffer loss of appetite and self neglect. In these cases 'mixed' vitamin deficiency syndromes are more common and respond better to vitamin B-complex treatment (Carney, 1971). Multiple vitamin B deficiencies including thiamine, pyridoxine and cyanocobalamin can result in polyneuropathy of varying manifestation. In Cuba in late 1992 and early 1993 there was an outbreak of a B vitamin deficiency related polyneuropathy affecting 50 000 people. It was reported to be a combination of a nutritional problem associated with possibly a toxic substance (WHO Press Release, September 1993). Thiamine deficiency is also seen in association with certain diseases: dysentery, diarrhea, cancer, liver diseases, infections and hyperthyroidism.

In refugee populations

Outbreaks of thiamine deficiency in refugees occurred in Cambodian refugees in Thailand in the beginning 1980's and more recently in Bhutanese refugees in Nepal in 1993–1995. A few cases were reported in Liberian refugees in Guinea (1990), in Eastern Ethiopia (1993) and in Djibouti (1993-1994). Table 1 summarises some of the recent outbreaks of thiamine deficiency among refugee populations. The outbreaks were always associated with rice-based diets lacking in variety. In Djibouti, children under five and women of childbearing age were most affected (RNIS, ACC/SCN No.2, Dec.93). The outbreak was brought under control as a result of thiamine supplementation and the addition of fortified corn soy blend to the ration. Cases of infantile beriberi and thiamine deficiency in pregnant women were also reported by MSF-F (1992) among the Karen refugee population in the Mae Sod Region, Thailand.

Rations of polished rice, oil and beans have a thiamine content of approximately 0.7 mg per day

Table 1. Thiamine deficiency in refugee populations

Year	Location	Population	Prevalence (%)
1980[a,b]	Thailand (Cambodian refugees)	-----	8% in adults only
1981[c]	"	60 000	5%
1982[a]	"	----	-----
1985[d]	"	----	-----
1992[e]	Thailand (Karen refugees)	----	6% of breast-feeding women/cases of infantile beriberi
1990[c]	Guinea (Liberian refugees)	200 000	few cases
1993[f]	Eastern Ethiopia (Djibouti/Somalia border)	----	few cases
1993/94[f]	Djibouti	10 000	142 cases
Oct.'93-June'94 [f,g]	Nepal (Bhutanese refugees)	85 000	12000 suspected cases
June'95	''	----	0.005/10000/day
Aug.'95	''	----	1.83/10000/day
Oct.'95	''	----	0.85/10000/day

[a] Berry-Koch et al 1990; [b] Dahlberg, 1980; [c] Clugston, 1994; [d] Toole, 1992; [e] MSF/Epicentre, 1992;
[f] RNIS reports #1,2,4,7,8,13. ACC/SCN News. Oct'93-Dec.'95.; [g] SCF(UK) Nepal reports.

(see Table 2). A ration should contain a minimum of 0.9 mg thiamine which does not provide for preparation and cooking losses. Blended food e.g. CSB (corn soy blend) contains 0.6 mg to 0.8 mg of thiamine per 100 g. A hundred grams of CSB would need to be added to the daily ration for the RDA of thiamine to be covered providing also for preparation and cooking losses.

Table 2. Thiamine content of a rice-based ration

	Quantity (g) per day	Thiamine content (mg)
Rice, polished	400	0.4
Vegetable oil	30	--
Beans	40	0.25

Source: Toole, 1994.

In Nepal, the first symptoms of thiamine deficiency appeared in the adult refugee population after the majority had been residing in the camp for 12 - 24 months. All reported cases of suspected thiamine deficiency appeared to be thiamine deficiency with peripheral neuropathy (dry beriberi). From October 1993 to June 1994, 12000 suspected thiamine deficiency cases had been reported of whom 10700 were mild and 1300 were severe cases. Mild cases were defined as those who reported to the refugee health centres with tingling and/or burning sensation and numbness. Severe cases were defined as those who reported to the health centres with weakness of limbs, ataxia, oedema, breathlessness and cardiac problems. Over 80% of the severe cases completely recovered with vitamin B complex administration and the rest responded to the treatment only partially. Those who did not improve had other medical problems as well, for example, cirrhosis of liver.

Usually thiamine deficiency develops within 12 weeks of a deficient intake. However, in the above mentioned refugee population, fresh vegetables and lentils had been provided consistently and symptoms of a deficiency appeared at a later stage than expected if the diet were totally lacking in thiamine.

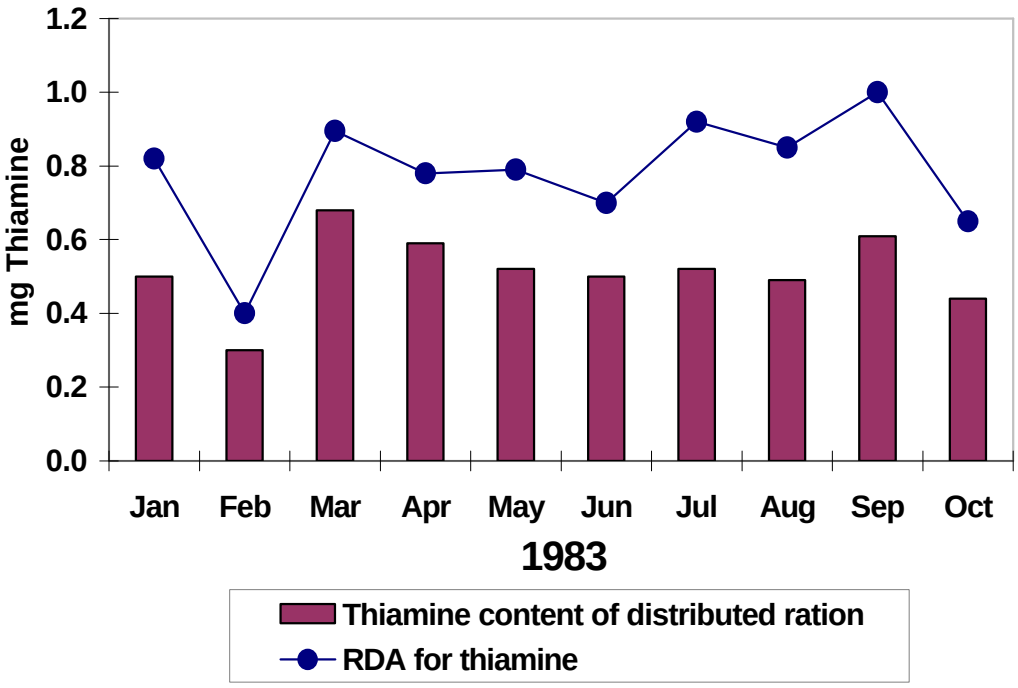
The thiamine content of the general ration that was distributed at the time is outlined in Table 3. Figure 1 shows the thiamine content of the ration in relation to the RDA for thiamine based on the energy content of the ration distributed. As shown, the thiamine content of the rations distributed were always lower than the minimum required.

An extensive nutrition survey was carried out to investigate the outbreak of thiamine deficiency in Bhutanese refugees in Nepal (SCF Nepal, J. Robertson, Jan. 9, 1994). About half of the refugees exchanged or sold some ration on a regular basis. Most did not like the red lentils in the ration and exchanged or sold it for meat or eggs, milk or curd, and vegetables, as well as for non-food items. The custom of extensive washing of rice prior to cooking reduced the little thiamine present in rice. Tea was the main drink consumed by both children and adults. Tannin in tea has been reported to inhibit thiamine absorption. There were no obvious toxins that could have been linked to the widespread polyneuropathy seen. There were no reported cases of thiamine deficiency in children, however, a number of school children had visual impairment. Most improved after being given vitamin B complex injections.

Table 3. Thiamine content of general ration distributed in Nepal in 1993

	Quantity (g/ person/day)	Thiamine content (mg)
Rice, polished	430	0.43
Lentils (red)	60	0.38
Oil	25	---
Sugar	20	---
Salt	5	---
Vegetables/Condiments	100	varying

Figure 1. Thiamine content of general ration in relation to RDA for thiamine based on energy content of the ration distributed



Note: The RDA for thiamine based on the energy intake is 0.4 mg/ 1000 kcal

The decline in thiamine deficiency seemed to be the combined effect of including parboiled rice (thiamine content higher than polished rice), 40 g of *unilitho* (blended food with a thiamine content of 0.1 mg per 100 g), a different variety of lentils and the continuation of vegetables (Clugston, 1994). A vigorous nutrition education programme had also been started (see annex for nutrition messages used which also contributed to the improvements seen).

Risk factors

The great outbreaks of thiamine deficiency in South-East Asia at the beginning of this century followed the large scale production of milled rice and its large scale distribution. The availability of milled rice as a cheap and popular food in urban areas was also a factor of importance for the occurrence of thiamine deficiency in those areas. The requirement of thiamine is increased when carbohydrates are taken in large amounts and is raised during periods of increased metabolism, for example, fever, muscular activity, hyperthyroidism and also during pregnancy and lactation. A diet based on polished rice is high in carbohydrates which augments the thiamine requirement and is compounded by a low thiamine content.

The overt risk factors reported by Rolfe and others (1993) in The Gambia were pregnancy, alcohol consumption, fevers, chronic disability, exercise, diabetes and dysentery. Polished rice consumption accounted for 44% of the total daily calorie consumption. In the rainy season there was increased

energy expenditure due to intense agricultural activity which raised thiamine requirements and depleted the body's already limited store of thiamine. Thiamine is water soluble and heat-labile and most of the vitamin is lost when the rice is washed and when the cooking water is discarded. Anti-thiamine factors, such as mycotoxins and thiaminases are often found in stored food especially during the humid rainy season.

MSF/Epicentre (1992) conducted a study of the food habits of breast-feeding women among the Karen refugee population with suspect clinical thiamine deficiency. Women with signs of thiamine deficiency were less likely to purchase foodstuffs in the camp stores and were less likely to consume raw vegetables at mealtimes than women without signs. The general ration distributed to the refugees was sufficient in calories (2048 kcal) with 89% coming from carbohydrates, 8% from proteins and 3% from fat. The thiamine content of the ration was 0.55 mg daily which was clearly below the requirement of 0.4 mg/1000 kcal. The staple, polished rice, was washed before boiling, sometimes up to three times, and the large quantity of water in which the rice was cooked was discarded thus depleting the rice of the small quantities of thiamine present. The breast-feeding women with signs of thiamine deficiency were also more likely to be subject to dietary taboos further limiting their intakes of thiamine. In addition, most women chewed betel nut, which is known to contain thiaminase, usually immediately after a meal. Another source of thiaminase was the raw fermented fish paste which was the main ingredient of the sauce eaten along with the rice.

Thiamine deficiency

Signs and symptoms

Adult thiamine deficiency

Thiamine deficiency with peripheral neuropathy
An acute form of thiamine deficiency characterized by polyneuropathy with paraesthesia of the extremities (especially the legs), reduced knee jerk and other tendon reflexes, and progressive severe weakness and wasting of muscles; the susceptibility to infections is greatly increased.
***Synonyms*:** atrophic beriberi; dietetic neuritis (in part); dry beriberi; endemic polyneuritis; panneuritis endemica; paralytic beriberi; polyneuritis endemica.

Thiamine deficiency with cardiopathy
An acute form of thiamine deficiency characterized by oedema (especially of the legs, but also involving the trunk and the face), high cardiac output, ventricular failure, sinus rhythm, dilatation of arterioles, depressed erythrocyte and leukocyte transketolase, elevated serum lactate and pyruvate, and pulmonary congestion with pleural effusions; death from congestive heart failure may occur abruptly. A less common fulminating form is characterized by lactic acidosis, hypotension, tachycardia, and pulmonary oedema (which is the cause of death); this is termed **thiamine deficiency with lactic acidosis**.
***Synonyms*:** beriberi heart disease (in part), cardiovascular beriberi; Shoshin beriberi (for the form with lactic acidosis); wet beriberi; wet dropsy.

Source: International Nomenclature of Diseases. Vol. IV Metabolic, Nutritional, and Endocrine Disorders. WHO Geneva 1991 pg 278.

It is difficult to speak of specific clinical symptoms of thiamine deficiency because of the variations of the clinical signs brought about by the presence of complicating factors, such as infections, or by the presence of symptoms from multiple deficiencies such as other B vitamins, vitamin C and

minerals as well as the effects of stresses of many kinds, such as physical labour and pregnancy.

The clinical picture of thiamine deficiency is, however, usually divided into a dry (neuritic) type and a wet (cardiac) type (see box above). The disease is wet or dry depending on the amount of fluid which accumulates in the body due to factors like cardiac function, kidney lesions, etc. even though the exact cause for this oedema has never been successfully explained. Many cases of thiamine deficiency show a mixture of the two main features and are more properly termed **thiamine deficiency with cardiopathy and peripheral neuropathy** (WHO, 1991).

The disease manifests itself principally with changes involving the nervous system, the cardiovascular system, and also the gastrointestinal tract (Williams, 1961; Sebrell, 1962; Sauberlich, 1967; WHO, 1976).

Nervous system: The most striking clinical signs of thiamine deficiency are related to the nervous system. Polyneuritis and paralysis of the peripheral nerves predominate. Manifestations are seen in the autonomic, the sensory, and the motor systems. In the *sensory system* tactile sensation is first affected, then there is pain, and finally temperature sensitivity is altered. They include loss of vibratory sense over the big toe and the ankle and disturbances in peripheral sensation such as paraesthesia (tingling, burning, numbness) in the legs and toes and superficial hyperesthesia (increased sensitivity) beginning in the lower extremities, then in the fingers tips, lower abdomen, and perioral areas and gradually expanding. The sensory effects are usually symmetrical although the side that is in greater use may be affected first.

Paralysis of the *motor nerves* occurs after the sensory disturbances. This also begins in the tips of the lower extremities, then in the fingers, and ascends progressively. There is increasing muscular weakness which is readily demonstrated by the inability of the individual to rise from a squatting position without assistance and, as the disease progresses, there is atrophy of the leg muscles. The tendon reflexes are also affected especially with loss of ankle and knee jerks. Painful calf muscles and, eventually, foot drop and, later, wrist drop may also develop. Advanced neurological changes may result in great difficulty in walking and may even lead to complete paralysis.

Cardiovascular system: The changes in the cardiovascular system may be serious and extensive. Frequent complaints are palpitation, weakness, and shortness of breath. Palpitation is related to tachycardia (rapid heart beat), and there may be a feeling of heart consciousness or of pain over the heart. These symptoms may occur quite early in the disease and electro-cardiographic changes are found in many cases. In the more severe deficiency, the heart is enlarged to the right, and there may be dizziness and low blood pressure. Changes in the heart muscle and accumulation of fluid between the muscle fibres have been seen. Patients with severe beriberi may die suddenly of heart failure or following exertion.

The state in which the thiamine deficient patient has developed acute heart failure has been termed '*Shoshin*' which means 'sudden collapse' in Japanese. The onset is sudden. The pulse is rapid; the diastolic pressure drops; the heart size increases; heart sounds are intensified and slight murmurs are often heard; the lungs show signs of congestion; the liver size increases; and the patient is nauseated and vomits. Cyanosis (blueness of skin due to a lack of oxygen) may be noted in the face. Consciousness is not lost at any time until the patient dies. Shoshin has more frequently been observed in adult men but has also been observed among pregnant and lactating women.

Gastrointestinal tract: The symptoms seem to be related primarily to the delayed emptying of the stomach and dilation of the colon. Loss of appetite (anorexia), vague abdominal complaints, and constipation are common manifestations. As the disease progresses nausea and vomiting may occur.

Williams (1961) reported that thiamine deficiency usually presented a symptom complex with three main features: (1) those of peripheral neuritis; (2) those of cardiac insufficiency; and (3) a generalized tendency to oedema. Among a large number of cases of thiamine deficiency every possible blend of these three sets of symptoms were encountered. Important additional signs accompanying the peripheral neuropathy are fatigue, decreased attention span and impaired capacity to work.

Unfortunately only a few objective methods exist to determine thiamine deficiency clinically. There is often some doubt as to the significance of clinical signs since the examination is by its nature subjective. Thiamine deficiency is a deficiency disease which involves so many bodily functions which manifest themselves in various ways that a specific clinical assessment protocol cannot be developed for the field. Table 4 attempts to summarize some of the typical lesions seen in specific organ systems of the body as a result of thiamine deficiency in adults.

Table 4. Organ Systems of the body affected in adult thiamine deficiency

Organ System of the body	Typical lesion
Heart and blood vessels	Enlarged heart. Congestive heart failure which is one of the contributory causes of *peripheral oedema* and results in increase in circulating blood volume.
Nervous system	Polyneuritis; autonomic, sensory and motor nerves are affected; paraesthesia and hyperesthesia, loss of ankle and knee jerks with muscle wasting and paralysis - typically wrist- and foot-drop (symmetrical).
Eye	Nutritional amblyopia (evidence suggests that thiamine deficiency may be one of the causes).
Gastrointestinal tract	Constipation (rarely diarrhea) with abdominal distension and colicky pains. Anorexia, nausea, vomiting.

MSF/Epicentre (1992) defined a suspect case of thiamine deficiency in the field as a person having at least two of the following signs:
- bilateral oedema of the lower limbs;
- dyspnea with exertion or at rest;
- paraesthesias of the extremities (hands or feet) or a symmetrical drop in muscular strength or motor deficiencies: stepping or loss of balance.

SCF (UK) used the following case definition for thiamine deficiency when carrying out their survey in Nepal in 1993:
C Severe cases:

- those with numbness and/or burning and/or tingling sensations;
- weakness of limbs, and ataxia;
- with or without: fever, oedema, neurological symptoms, loss of consciousness, vomiting or sensory impairment (vision or hearing);
- and resulting in: residual muscular weakness and/or paralysis or recovery, or death.

C Mild cases:
- those suffering from peripheral neuropathy alone.

Infantile thiamine deficiency

Thiamine deficiency in infants, which is rarely seen today, is almost invariably an acute disease which mainly affected infants breast-fed by women having deficient thiamine levels (see also section ‘ Thiamine in breastmilk’). The onset of the symptoms is often very rapid and the fatality rate is very high (see section on outbreaks): death often occurs within a few days of the onset of detected symptoms. Initially the infant is usually of normal appearance with varying degrees of constipation, occasional vomiting, crying and restlessness. The disease usually presents with generalized oedema, dyspnoea (difficulty in breathing), cardiac disturbance, gastrointestinal derangements, and oliguria (diminished secretion of urine), the symptoms varying in relative intensity in each individual case. Sebrell (1962) described three main types of infantile thiamine deficiency depending also on the age of the infant:

Pure cardiologic* or *pernicious form
The infant shows signs of cyanosis and an acute cardiac attack can follow with the infant usually dying within 2 to 4 hours. The common age for this form of the deficiency disease is one month up through the third month. It has been reported that this type of deficiency responds very dramatically to thiamine.

Aphonic form
A milder form of infantile beriberi which causes a typical loss of voice due to paresis or even paralysis of the vocal cords due to neuritis is more frequent in the age group 4 to 6 months..

Pseudo meningitic form.
Older infants (7 to 9 months), in particular, may manifest symptoms that can be mistaken for bacterial meningitis eg. stiffness of neck and other apparent signs of meningeal irritation accompanied by vomiting, convulsions and sweating.

Infantile beriberi must be suspected in a population if there is a high incidence of death in the second to fifth months of life. Normally, in a population, there is a steep decrease in infant mortality throughout the first 6 months. The typical feature of infantile beriberi is that instead of infant mortality decreasing after the first month, it remains high or even increases to a peak at about the 3rd month.

Wernicke-Korsakov Syndrome

This syndrome, which is rarely seen in the Orient, occurs primarily in alcoholics, half of whom have

liver disease, and is often precipitated abruptly by administration of glucose to patients severely deficient in thiamine. If untreated, death is common; even with treatment, 17% die within 3 weeks (Feldmann, 1988). Only a minority of chronic alcoholics develop the disease, since it is only seen in patients with a genetic abnormality in the thiamine-dependent enzyme, transketolase. The syndrome does not develop during famine and starvation.

Wernicke-Korsakov syndrome

A thiamine-deficiency syndrome characterized by symmetric hyperaemic lesions of the brainstem, hypothalamus, thalamus, and mamillary bodies with glial proliferation, capillary dilatation, and perivascular haemorrhage. The syndrome is manifested by a confusional state, disorientation, ophthalmoplegia, nystagmus, diplopia, and ataxia (Wernicke encephalopathy), with severe loss of memory for recent events and confabulation (the invention of accounts of events to cover the loss of memory) (Korsakov psychosis) occurring following recovery. Defective binding of thiamine diphosphate by transketolase has been found. It appears that the disorder is of autosomal recessive inheritance but is expressed as clinical disease only in the event of thiamine deficiency.
Note. The encephalopathy described in the first part of the definition was first reported by Wernicke in 1881, and the psychosis was reported by Korsakov in 1887. These two disorders are of a single pathological entity due to thiamine deficiency which arises most frequently in alcoholics.

Source: International Nomenclature of Diseases. Vol. IV Metabolic, Nutritional, and Endocrine Disorders. WHO, Geneva 1991 pg 278–279.

Neurological changes affect the central nervous system. The following symptoms are usually observed:

- global confusion, not oriented to place and time ranging from mild confusion to coma;
- apathy with psychomotor retardation and lack of insight;
- impaired retentive memory and cognitive function;
- confabulation (readiness to answer any question fluently with no regard whatever to facts);
- incoordination and ataxia involving principally the lower extremities varying in severity; and
- nystagmus (rhythmical oscillation of the eyeballs, either horizontal, rotary or vertical).

It should be noted, however, that these are not exclusively symptoms of thiamine deficiency.

Excessive alcohol intake appears to affect the thiamine status in three main ways (Combs,1992):

- The diets of alcoholics are frequently low in thiamine, a large percentage of the daily energy intake being displaced by nutrient-deficient alcoholic beverages.
- The metabolic demands for thiamine are increased by the consumption of a diet rich in carbohydrates as a primary source of energy.
- Alcohol can inhibit the intestinal ATPase involved in the enteric absorption of thiamine.

However, the Wernicke-Korsakoff syndrome is not confined to alcoholics and can result also from unsupervised, self-prescribed weight reduction.

Subclinical thiamine deficiency

Although frank thiamine deficiency is rare today, large segments of the world's population continue to subsist on marginal or sub-marginal intakes of thiamine (Sauberlich, 1967; Kawai et al,1980; Lonsdale et al,1980; Anderson et al,1985; Barrett et al,1992). People exposed to subclinical

thiamine deficiency are predisposed to manifest frank beriberi under appropriate circumstances, occasionally in epidemic proportions (Tang et al, 1989; Rolfe et al,1993). These population groups with endemic subclinical deficiency are frequently difficult to identify because of the lack of quick and simple means of assessing subclinical thiamine deficiency.

Body storage of thiamine is minimal, the liver being the main extra-muscular storage site. In young and healthy non-alcoholic individuals, subjective symptoms appear after 2 to 3 weeks of a deficient diet (Brin,1963). Characteristic early symptoms include anorexia, weakness, aching, burning sensation in hands and feet, indigestion, irritability and depression. After 6 to 8 weeks the only objective signs at rest may be a slight fall in blood pressure, and moderate weight loss. After 2 to 3 months apathy and weakness become extreme, calf muscle tenderness develops with loss of recent memory, confusion, ataxia and sometimes persistent vomiting (Anderson et al,1985).

Mild thiamine deficiency can be seen in people who have *high carbohydrate intakes* and *low thiamine intakes* e.g. in people whose staple food is polished rice, especially if their diet contains anti-thiamine factors (tea, coffee, betel nuts, raw fermented fish) and in population groups who consume large quantities of refined carbohydrates in the form of sweetened carbonated drinks and candies. High alcohol intakes and continuous high-calorie intravenous feeding can lead to detectable thiamine deficiency. At risk are also groups whose *minimum thiamine needs* are markedly *increased* because of raised physiological or metabolic demand (Anderson et al,1985):

- pregnancy and lactation
- heavy physical exertion
- intercurrent illness (cancer, liver diseases, infections, hyperthyroidism)
- surgery

and wherever *absorption is reduced* by:

- regular high blood alcohol levels
- gastrointestinal disease; dysentery, diarrhoea, nausea/vomiting.

The symptoms of mild thiamine deficiency are vague and can be attributed to other problems, so that diagnosis is often difficult. Marks (1975) reported that a useful sign of mild and moderate thiamine deficiency is myotactic irritability. Anorexia, which is one of the early symptoms of subclinical thiamine deficiency, is regarded to be a protective phenomenon since a high-carbohydrate diet is most dangerous in the presence of thiamine deficiency (Lonsdale et al,1980).

The symptoms of mild thiamine deficiency clinically improve by the administration of thiamine. Lonsdale (1980) however, reported that in his patients who were biochemically thiamine deficient and who had symptoms considered generally to be those of neuritic dysfunction, the reversal of the metabolic disturbance occurred much slower than is generally associated with vitamin deficiency states.

Abnormal biochemical thiamine status has been associated with reduced growth in the young (Neumann et al, 1979), chronic ill-health in young or middle aged adults (Lonsdale et al, 1980), falls and fractures in old age (Older et al, 1982), impaired reaction to stress such as surgery (Alvarex et al, 1982), lactic acidosis, renal dysfunction, endocarditis, arrhythmias, sudden death in adults (Campbell, 1984; Anderson et al, 1985) and with the Sudden Infant Death Syndrome (Jeffrey et al, 1985). Experiments have also shown that thiamine deficiency predisposes to infection (Anderson et al, 1986).

Biochemical detection of thiamine deficiency

The diagnosis of beriberi is assisted by a dietary history suggestive of a low thiamine intake and clinical manifestations. However, objective biochemical tests of thiamine status, particularly measurement of erythrocyte transketolase activity (ETKA) and the thiamine pyrophosphate effect (TPPE), provide a sensitive test for thiamine deficiency where there are laboratory facilities available (Sauberlich, 1967).

Determinations of free thiamine in blood plasma do not necessarily reflect a direct relationship to the level in the tissues. Erythrocyte or leucocyte thiamine values apparently show a more direct relationship to tissue content (Feldman, 1980). Therefore, erythrocyte transketolase activity, the activity of the thiamine-requiring enzyme transketolase, appears to provide information as to tissue reserves of thiamine and reflects a direct functional evaluation at the cellular level. The assay for transketolase, TPPE, is performed in the absence and the presence of added thiamine and expressed as an activity coefficient. Values without added thiamine reflect the amount of coenzyme present in the cells. The stimulation with added thiamine pyrophosphate gives the measure of apoenzyme present that lacks coenzyme. TPPE is expressed as the percentage increase in ETKA obtained after addition of TPP to the erythrocyte. The biochemical diagnostic criteria of thiamine deficiency consist of low ETKA (normal values range from 42.1 to 86.1 mF/litre/min) and high TPPE (normal range 0-14%; see also Table 5).

Table 5. Classification of thiamine pyrophosphate effect (TPPE) in individuals

Thiamine condition	TPPE
Normal	0–14 %
Marginally deficient	15–24 %
Severely deficient (with clinical signs)	25+ %

Source: Brin et al(1965)

Urinary thiamine levels can provide information as to the adequacy of the dietary intakes, but they do not provide the desired information regarding the state of deficiency or the degree of depletion of tissue thiamine reserves. At recommended intakes, urinary excretion of thiamine ranges from 40 to 90 Fg per day. When intake is deficient, urinary excretion falls below 25 Fg per day. A correlation between the urinary excretion of thiamine per gram of creatinine and thiamine intake has been observed. See Table 6 for a summary of the interpretive guidelines for the urinary excretion of thiamine. Analyses of 24-hour urine collections provide more reliable information than random sample collections. In cases of clinical thiamine deficiency, 24-hour urinary excretion of 0 to 15 Fg of thiamine have been reported (Sauberlich, 1974). Additional information as to the physiological state with respect to thiamine can be obtained from the test-dose procedure. The most commonly used procedure is to administer parenterally 5 mg of thiamine and measure the urinary excretion of thiamine over the following 4-hour period (see Table 6). In the field, this test dose procedure has not been used extensively because of the inconvenience in obtaining 4-hour urine collection following the administration of the thiamine test load. Although the test may not specifically identify clinical thiamine deficiency or indicate the severity of the deficiency, it can be useful as an indicator of low intakes and tissue deficits of the vitamin (Sauberlich, 1974).

Table 6. Guidelines for the interpretation of urinary excretion of thiamine

Subjects	Deficient (high risk)	Low (medium risk)	Acceptable (low risk)
Urinary thiamine, Fg/g creatinine			
1 to 3 years	< 120	120–175	176
4 to 6 years	< 85	85–120	121
7 to 9 years	<70	70–180	181
10 to 12 years	<60	60–180	181
13 to 15 years	< 50	50–150	151
adults	< 27	27–65	66
pregnancy			
2nd trimester	<23	23–54	55
3rd trimester	<21	21–49	50
Urinary thiamine , Fg per 6 or 24 hours			
adults: per 24 hr	< 40	40–99	100
per 6 hr	< 10	10-24	25
Load test (return of 5 mg thiamine dose)			
adults: % return of thiamine load in 4hr	< 20	20–79	80

Source: Adapted from Sauberlich HE, Skala JH, Dowdy RP. Laboratory tests for the assessment of nutritional status. Cleveland, Ohio, CRC Press, 1974.

The following gives a summary of the biochemical methods used to assess thiamine status in humans:

- *Blood thiamine*: Blood contains only about 0.8% of the total body thiamine, and the concentration is too low to allow precise extrapolation of the total thiamine status. There is, however, a relatively accurate microbiological method which can be used with whole blood, red and white blood cells, or any other body fluids and tissues.

- *Urinary thiamine excretion*: The measurement of urinary thiamine excretion is not a very reliable method for assessing tissue stores, and analogous to the blood levels, is really only a reflection of the immediately preceding intake. Clinical signs of deficiency have been noted when less than 7% (70 Fg) of a 1 mg dose of thiamine is excreted in the urine in a dose-retention test (National Research Council [U.S.], 1989).

- *Pyruvate and lactate*: Thiamine is required for pyruvate metabolism; increased blood pyruvate and lactate levels can be caused by thiamine deficiency. In thiamine deficiency, the fasting levels of blood pyruvate have frequently been found to be normal and only rise above the normal following a glucose load (Sauberlich, 1967). The estimation of blood pyruvate can be of help in the diagnosis of suspected thiamine deficiency. It is, however, not appropriate for the detection of marginal thiamine deficiencies in view of limits in the sensitivity of this index. An elevated pyruvate level is also not always attributable to thiamine deficiency.

- *Transketolase activity / thiamine pyrophosphate effect*: One of the most reliable indicators of thiamine functional status is the activity of the thiamine-requiring enzyme transketolase. The level of transketolase activity allows for judgement on the availability of thiamine.

Table 7 summarises the proposed guidelines and cut-offs for differentiating the levels of risk of thiamine deficiency in a population using various criteria.

Table 7. Proposed criteria for assessing public health significance of thiamine deficiency in populations

	Severity of public health problem*		
Indicator	**Mild**	**Moderate**	**Severe**
Clinical signs:	$1 clinical case; <1% of population	1-4% of population	$5% of population
TPPE test >25%:	5-19 %	20-49 %	$50 %
Urinary thiamine per g creatinine:*	5-19 %	20-49 %	$50 %
Breastmilk thiamine** (< 50 µg/l)	5-19 %	20-49 %	$50 %
Dietary intake : (<0.33 mg/1000 kcal)	5-19%	20-49%	$50 %
Infant mortality (between 2nd and 5th months)	No decline in rates	Slight peak in rates	Marked peak in rates

* expressed as percent of population for each age group, see Table 6 for cut-offs used.

** a. see also section "Thiamine in breast milk", page 26.
b. TPPE test easier to perform (personal communication, H.E. Sauberlich, October 1999).

History

Outbreaks

Thiamine deficiency was first recognized in China as early as 2600 BC and was documented in the oldest medical treatise extant, a Chinese text of the second millennium BC (Marks, 1975). A Dutch physician observed it in the East Indies in 1645, and a British physician gave a detailed account of its occurrence in an area on the east coast of India in 1835 (Aykroyd, 1970). There are other early references that have been recorded in historical studies but it was in the 1870's that thiamine deficiency became a common disease in many parts of South-East Asia, causing much disability and a high mortality. It remained a problem in South-East Asia until the 1930s.

In countries where polished rice is the main dietary constituent, biochemical thiamine deficiency is prevalent among the population even if frank clinical thiamine deficiency has become rare. The incidence may be augmented by anti-thiamine factors in the diet that are present in e.g. tea leaves, herring, shellfish, raw carp, fermented fish, betel nuts (Vimokesant et al, 1975; Kositawattanakul et al, 1977; Vimokesant et al, 1982).

To understand the extent of the problem that thiamine deficiency caused it is necessary to look at some of the countries that were affected:

Japan:
Thiamine deficiency was prevalent in urban areas at the end of the 19th century but soon spread to smaller towns and rural areas. In 1878, Kyoto, a city of 230,000 people at that time, reported 1093 cases of beriberi which was probably too low a figure. The incidence in the Japanese army, where statistics were more carefully kept, was much higher. In 1875, 26% of the entire army of 17,500 had thiamine deficiency (Williams, 1961). In 1925, the death rate from infantile thiamine deficiency was 3.5 per 1000 live births (Sebrell, 1952). In 1923, over 20 thousand people are said to have died of shoshin (sudden collapse) beriberi (Kawai et al,1980). Serious outbreaks of thiamine deficiency occurred in prison camps in Japanese-occupied countries during the Second World War because of the restricted rice diet given to the prisoners.

In 1965, an authoritative report pronounced thiamine deficiency extinct in Japan thanks to improved post-war nutrition. However, in the mid 1970's reports concerning a puzzling association between various combinations of oedema, carditis and neuritis were made and a total of 399 cases of frank thiamine deficiency were documented in the period of 4 years (Anderson et al,1985). Many of the documented cases with thiamine deficiency heart disease were adolescents who had regularly consumed excessive amounts of carbohydrates such as sweet carbonated soft drinks, instant noodles and highly-polished rice, all lacking thiamine and leading to relative thiamine deficiency. The daily intake of thiamine was reported to have been between 0.28 and 0.98 mg (Kawai et al,1980). A sudden increase in thiamine requirements due to strenuous exercise had resulted in overt thiamine deficiency heart disease.

Philippines:
In 1910, about 40% of the infants born in the city of Manila died of thiamine deficiency usually at 2–5 months of age. In 1948, 1580 cases of frank or suspected thiamine deficiency were found out of a total of 12,384 people examined (12.7%) in the province Bataan. Infantile thiamine deficiency

consistently represented 70-80% of the total number of infant deaths recorded as caused by thiamine deficiency. For the period from 1954 to 1958, 15200 infant deaths were reported to be due to infantile thiamine deficiency, while 6030 deaths occurred among older groups (total mortality rate of 95.9 per 100,000 population). Thiamine deficiency ranked as the fourth leading cause of death in the Philippines, exceeded only by pneumonia, tuberculosis, and bronchitis (Williams, 1961).

Malaysia (Malaya):
150,000 cases of thiamine deficiency had been treated in government hospitals during a 20-year period, and 30,000 people died from it out of a population of 1,250,000. At the beginning of the century there were three communities in the country—the indigenous Malays living mainly in villages near the coast, the Tamils from South India working on rubber estates, and Chinese immigrant labourers working in tin mines. Rice was the staple cereal of all three communities but the rice was processed differently by each community (see Table 8). The Malays grew their own rice and consumed it after home-pounding, which meant dehusked and not highly polished; the Tamils ate parboiled rice; the Chinese labourers ate white polished rice imported from Thailand which was provided by the employers in unlimited amounts as part of their wages. The last group obtained 2500–3200 calories a day from milled rice alone with few opportunities of supplementing the rice (Burgess, 1958). The Chinese labour force was extremely prone to thiamine deficiency. It was estimated that out of every 1000 inhabitants, 120 had had some degree of thiamine deficiency, 80 had had severe thiamine deficiency and 16 had died. In Kuala Lumpur, then a mining town, a hospital with 14 wards was built; eight of these were reserved for patients with thiamine deficiency (Aykroyd,1970).

Table 8. Contrast in types of rice used and the incidence of thiamine deficiency

Community	Kind of rice used	Incidence of thiamine deficiency
Malays	Home pounded	Rare
Tamils	Parboiled	None
Chinese	Imported white rice	Very high
Europeans	Little rice consumed	None

Singapore:
Lee (1994) reported that thiamine deficiency had been endemic among the patients in a lunatic asylum with a high mortality rate. In 1896, 40 of the 85 deaths in the asylum were due to thiamine deficiency; and in 1898, 55 out of 95. Because of ignorance of the causes of thiamine deficiency, a 'specialized' thiamine deficiency hospital was established in 1907 to cope with the high incidence of the deficiency disease. The treatment was empirical depending on which hypothesis the doctor believed in: that the disease was either caused by an infection or by a poison. In 1899, there were 453 admissions to the hospital with 304 deaths. In 1904, a trial was conducted to see whether eating parboiled rice could prevent thiamine deficiency which resulted in a great reduction in the incidence of thiamine deficiency. The hospital subsequently closed in 1925 having had only 50 admissions the previous year.

Other countries in South-East Asia:
During the period 1895-1904 it has been estimated that there may well have been 10 million cases of thiamine deficiency in China (Williams, 1961). In 1910, the health officer of Bangkok estimated 22670 cases with 1063 deaths in Bangkok. In 1895, there was a report of an epidemic in an mental asylum in Rangoon, Burma in which 211 cases appeared among 233 inmates.

Only three decades ago, the Chiengrai Province in Thailand reported a 24% incidence of peripheral neuropathy among adults and adolescents, and 3.7% of children admitted to the Pediatric Department of Chiengrai hospital were shown to have had thiamine deficiency (Thanangkul et al,1966). Infantile thiamine deficiency, until only recently, was a serious problem that accounted for a large number of deaths during the first months of life. It is the only serious form of malnutrition which occurs in the adequately breast-fed infant and this occurs only when the mother is herself thiamine deficient. In the beginning of the 1970s in Thailand, about 10% of 87 apparently healthy infants and children had evidence of biochemical thiamine deficiency (Pongpanich et al, 1974). Thiamine deficiency accompanied Chinese and Japanese labourers wherever they went and it was reported among them in Hawaii, Fiji, New Zealand and Australia.

Europe and North America:
Thiamine deficiency was also reported sporadically in many countries in the West especially in wheat (refined white flour) eaters in fishing communities. In 1890, it was reported in New England fishermen; in 1912, in Newfoundland and parts of southern Labrador. During the long winter months the villages where the fishermen and their families lived were isolated by snow and ice and they had to rely on stores bought in the capital; white flour, salted pork, molasses, margarine and tea with some dried salted cod. The white milled flour was the main source of calories. They lived on these foods throughout the winter and early spring and by April and May thiamine deficiency made its appearance (Akyroyd, 1970). An important feature was recurrence; some fishermen suffered regularly from thiamine deficiency year after year and often became crippled by peripheral neuritis.

Reports were also received of the disease in mental asylums in the United States. It was frequently reported among sailors arriving in all the large ports in the United States at the turn of the century. The term 'ship beriberi' was often used since in the West most of the thiamine deficiency cases were seen on ships. Studies document the appearance of the disease on a total of 158 different ships involving 947 persons of whom 147 died. Macpherson (1966) reported that at the turn of the century when scurvy had disappeared in the Norwegian merchant navy due to the provision of lime juice, white bread was introduced in place of the dark rye bread, and 'ship beriberi' became common, especially on long voyages. He also reports on an elderly captain who didn't get the disease since he preferred his rye bread to the white bread, who could cure his sailors who contracted the disease by providing them with rye bread.

Central and South America and Africa:
Thiamine deficiency rarely occurred in free-living populations in Central and South America, but did make some appearance in closed communities such as the Brazilian navy and workers engaged in constructing the Panama Canal. The same is true of Africa, where it has been largely confined to a few military and police forces (Aykroyd, 1970). However, in 1910, there was an account of a severe outbreak in the Ivory Coast in which about 900 persons or 80% of those affected died (Williams, 1961). These people ate no rice but lived on bananas, yams, corn, and vegetables. Two

studies in Ghana showed that 54% and 82% respectively of the children were thiamine deficient (Neumann et al, 1979). The gradual replacement of traditional cereals with imported milled rice has increased susceptibility to thiamine deficiency in many parts of Africa.

Past theories on causes and prevention

Until just over a century ago the prevailing view of the cause of thiamine deficiency was that it was due to an infection or a toxin. Theories regarding the cause of thiamine deficiency included that it was due to some deficiency in food, for example, a deficiency in fat and nitrogen. The treatment at the time was entirely symptomatic and ineffective, which of course reflected utter confusion regarding the aetiology of thiamine deficiency at that time. However, as early as 1859, the occurrence of thiamine deficiency in the Dutch East Indian navy was said to be due to poor rations. The ration of the native crews of the fleet consisted of 1000 g of rice and 300 g of meat. During the same time the European crew received: 400 g bread, 500 g rice, 400 g meat, 75 g lard, 35 g butter and 300 g beans, peas and potatoes. Thiamine deficiency was exceedingly common among the natives but rare among the Europeans (Williams, 1961). In 1874, native sailors were given the same rations as Europeans and the extent of thiamine deficiency decreased greatly.

The first person to show conclusively that thiamine deficiency is a nutritional disease, and to combat it by nutritional measures, was the Japanese naval surgeon Admiral Takaki. In 1878, a third of the Japanese navy suffered from thiamine deficiency; ten years later it had completely disappeared as a result of a change in the naval rations. Instead of a diet composed almost exclusively of milled rice the sailors were given wheat, barley, beans, milk, and meat, and only little rice. His findings were published in Japanese journals with limited circulation, therefore other rice-eating countries in Asia could not benefit from Takaki's achievement in reducing the problem of thiamine deficiency. It was only in the 1900's when the connection between thiamine
deficiency and milled rice had become more evident that studies on soldiers, police, and prisoners clearly demonstrated that replacing milled rice by under-milled rice and other foods prevented the disease.

Thiamine, the vitamin

Discovery

In the late 1890's, Dutch medical officers Eijkman and Grijns, working in Java, showed that a paralytic condition resembling beriberi could be produced in chickens by feeding them a diet consisting solely of polished rice (Jukes,1989). The rapidity with which chickens and pigeons develop polyneuritis on a diet of polished rice made them useful as test animals. They also showed that polyneuritis did not develop if the chickens were fed unpolished rice and that it could be prevented by administration of rice polishings to birds on the polished rice diet. They recognized the similarity of polyneuritis in birds and the disease beriberi in humans. Human experiments were carried out in a mental asylum and in railroad labour camps in the Malay States, whereby half of the subjects received polished rice, and the other half received brown rice, from which the polishings had not been removed (Williams, 1961). Beriberi always appeared in the white rice groups.

In 1926, Jansen and Donath, working in the laboratory formerly occupied by Eijkman, isolated the

anti-beriberi factor, vitamin B_1, as crystals from a water extract of rice bran. In 1936, Williams, who first began experimenting with vitamin B_1 in Manila around 1910, identified and published the chemical formula and named it *thiamine*, referring to the thiazole and amino groups in the molecule. A year later, improved methods of synthesis led to the first commercial production of the vitamin, thiamine.

Properties

Chemistry

The thiamine molecule is a water soluble, white crystalline solid. In the crystallized state or in an acid solution the stability of thiamine is good, even when heated. In a neutral or alkaline solution thiamine is unstable and sensitive to heat, oxygen and ultraviolet light.

Physiology and Metabolic function

Thiamine is rapidly and actively absorbed from the small intestine and is transformed within the body by phosphorylation into active co-enzyme thiamine pyrophosphate. The reaction can take place in most tissues but particularly in the liver cells. The blood level amounts to about 10 Fg/100 ml as thiamine pyrophosphate in the corpuscles and about 1 Fg as the free vitamin in plasma (Combs,1992).

Since the body is incapable of storing thiamine and the vitamin has a high turnover rate, a continuous supply of the vitamin is needed. The limited stores may be depleted within two weeks or less on a thiamine-free diet, with clinical signs appearing shortly thereafter. The body is readily depleted of thiamine by fever and other metabolic stress. The heart, kidney, liver and brain have the highest concentrations, followed by the leukocytes and the red blood cells (F. Hoffman-LaRoche, 1994). Dephosphorylation can occur in the kidney and excess free vitamin is rapidly excreted in the urine. The urinary excretion depends in part on the urine volume and during diuresis large amounts of thiamine may be lost. Small quantities of thiamine are excreted in sweat (Marks, 1975).

The metabolically active form of thiamine is thiamine pyrophosphate (TPP). Specific enzymes need TPP as an essential cofactor. TPP is essential for several biochemical reactions involved in the breakdown of glucose to liberate energy. TPP acts as a co-enzyme in oxidative decarboxylation and transketolase reactions. Thiamine is thus an important factor in carbohydrate metabolism and hence in thiamine deficiency blood pyruvate and often blood lactate levels rise steeply (Combs,1992).

Thiamine also plays a vital role in nerve function as is evidenced by the localization of signs of thiamine deprivation which are often mainly neurological. The biochemical nature of its role is still unclear, but it has been proposed that thiamine has a non-metabolic function related to nerve transmission.

Production and usage

Large scale commercial production of thiamine was carried out in the late 1930s after the identification of the chemical formula of the vitamin. In 1943, Williams and others carried out studies that documented the widespread deficiency of thiamine in the United States (Williams, 1961).

The two principal areas in which deficiencies occurred, besides Labrador and Newfoundland, were the low income rural people of the South and the slum inhabitants of large cities, especially alcoholics. It was shown that low intakes of thiamine, riboflavin, and niacin were, in substantial part, traceable to the predominance of the intake of refined white cereals in the diet. At about the same time standards for enriched flour were drawn up by the US Food and Nutrition Board, requiring that thiamine, niacin, riboflavin and iron be added to white flour (wheat and maize). The fortification of rice was undertaken in the southern States, where rice was the staple food.

In the late 1940's, Dr. Salcedo undertook what is now known as the 'Bataan experiment' in the Philippines. In the province, Bataan, 14.3% of the population had frank or suspected beriberi. Enriched rice, each pound of which provided 2 mg thiamine, 16 mg niacin and 13 mg iron, was introduced to a control group and the cases of beriberi dropped to 1.55% after two years. It was hoped that the success of this experiment would lead other rice-eating countries to enforce laws regarding the fortification of rice. The provision of whole flour as well as the thiamine enrichment of flour virtually eliminated thiamine deficiency in Newfoundland in the 1940s.

Today, several countries including Australia, Canada, Chile, Guatemala and the UK, have mandatory flour fortification laws; others ie. Switzerland, Brazil, Yemen, have optional laws (Nagy, 1996). Margarine enriched with thiamine is available in Chile and in Indonesia. Enriched soft drinks are available in Germany and the US. It is technically feasible to fortify with thiamine products such as: flour, meal, grits, rice, bread, cakes and biscuits, pasta, frozen and baked products (see also section on stability of thiamine in foods).

RDA (Recommended Daily Allowance) for thiamine

Calculating RDA for thiamine

Recommended daily allowances for thiamine have been based on the following:

- assessment of the effects of varying levels of dietary thiamine on the occurrence of clinical signs of deficiency;
- urinary excretion of thiamine;
- erythrocyte transketolase activity.

Several studies were undertaken in the 1940s and 1950s to come up with the minimum levels of thiamine intakes to prevent clinical signs from appearing. Table C, Annex 3 shows the results of some experimental human thiamine deficiency studies.

Thiamine requirements are closely related to carbohydrate intake. In rice diets, 75% or more of the energy is provided by carbohydrate. Thiamine needs have usually been expressed as mg per 1000 kcal energy from carbohydrate intake. However, the error involved in relating the thiamine content of a diet to the total energy content of the diet rather than to the energy derived from carbohydrate alone is minimal.

Foltz and others (1944) reported that thiamine deficiency occurred within 8 weeks in the majority of humans kept on an intake of 0.20 mg thiamine/1000 kcal or less (total intakes of 0.6 mg thiamine or less daily). The minimum requirement was stated as ranging from 0.33 to 0.45 mg thiamine/1000

kcal (1.0 to 1.5 mg thiamine daily) which was necessary for maintenance and for well-being. Anderson and others (1986) recommended a minimum thiamine intake of 1.22 mg/day for men and 1.03 mg/day for women. Values for thiamine intake ranging between 0.2 and 0.5 mg per 1000 kcal have been reported as those needed to satisfy requirements. The large differences can be explained by differences in approach and in experimental procedures used to estimate thiamine requirements.

Anderson and others (1986) reported that restricting thiamine intake to 0.45 mg/day for up to 6 months caused anorexia and eventually progressive general impairment of mental and physical health that took three months to respond fully to oral thiamine replacement.

Based on the urinary excretion of thiamine, a critical intake appears to be approximately 0.2 mg thiamine/1000 kcal, below which urinary excretion is low (5 to 20 Fg) and clinical signs of thiamine deficiency may appear. Studies suggest that the minimum requirement is 0.33 mg thiamine/1000 kcal, and that an intake of over 0.5 mg/1000 kcal is necessary for tissue saturation.

Normal red-cell transketolase activities have been observed in subjects consuming 0.4 mg/1000 kcal but at least 0.6 mg/1000 kcal of thiamine was necessary to obtain maximum activity (National Research Council [US], 1989).

RDA for adults

WHO (1967) states that the recommended intake for thiamine is 0.4 mg/1000 kcal. An adult man consuming 3200 kcal daily would therefore need a daily intake of 1.3 mg thiamine, whereas a woman consuming an average of 2300 kcal would require an intake of 0.9 mg thiamine daily. A thiamine allowance for adults of 0.5 mg/1000 kcal is recommended by the National Research Council [US] (1989) but they also recommend that the total daily intake should not be less than 1.0 mg even for those consuming less than 2000 kcal daily.

RDA for pregnancy and lactation

Table 9 summarises the requirements of thiamine during pregnancy and lactation (WHO, 1967). Higher levels have been recommended by the National Research Council [US] (1989): on the basis of an additional energy requirement of 300 kcal/day, an additional 0.4 mg/day is recommended throughout pregnancy. During lactation, an additional 0.5 mg/day is recommended to account for the thiamine loss in the milk and the increased energy consumption.

RDA for infants

Studies of the thiamine content of human milk suggest that the minimum daily requirement to protect against deficiency is approximately 0.17 mg/day. This estimate is based on the mean concentration of 0.23 mg thiamine/litre breast milk (Nail et al,1980) and a mean consumption of 750 ml breast milk daily by the infant. The requirement of 0.3 mg/litre, or 0.4 mg/1000 kcal was estimated from the mean thiamine concentration plus 2 standard deviations in breastmilk (WHO, 1967; American Academy of Pediatrics, 1985; National Research Council [US], 1989).

RDA for children and adolescents

WHO (1967) recommends the allowance of 0.4 mg/1000 kcal also for children and adolescents (see Table 9), whereas the National Research Council [US] recommends 0.5 mg/1000 kcal.

Table 9. Daily recommended intakes of thiamine

Age (years/population group)		Thiamine (mg)
Children:		
	under 1	0.3
	1-3	0.5
	4-6	0.7
	7-9	0.9
Male adolescents:		
	10-12	1.0
	13-15	1.2
	16-19	1.2
Female adolescents:		
	10-12	0.9
	13-15	1.0
	16-19	0.9
Adult man (moderately active)		1.2
Adult women (moderately active)		0.9
Pregnancy		+0.1
Lactation (first 6 months)		+0.2
Whole population (average)		0.9

Source: WHO (1974)

Factors affecting thiamine requirements

The following factors have been found to influence thiamine requirements (WHO, 1967):

- *Composition of the diet*
  Experimental studies with adults and infants have indicated that thiamine requirement is related to the dietary ratio of carbohydrates to fat. However, a major increase in the proportion of fat in the diet was found to have a comparatively small effect on thiamine requirements. Thus, diets exceedingly high in carbohydrates appear to increase the requirement for thiamine. Proteins in the diet play an intermediate role between fats and carbohydrates with regard to their metabolic influence on thiamine requirements (WHO, 1967).

  Carbohydrate and protein calories more closely represent the total calorie intake of people in developing countries. Although this fact may result in an increase in the thiamine required per 1 000 calories, the significance of this in humans is unknown.

- *Climate*
  Climatic changes involving cold or hot temperatures increase or decrease energy expenditure respectively and therefore increase or decrease requirements. This energywould have an effect

on the absolute requirement for thiamine. However the ratio of thiamine does not appear to change.

C *Body weight*
The thiamine requirement will vary with body weight to the extent that energy requirements are related to body weight. Table 10 shows the recommended thiamine intakes for adults of different body weights adjusted for body weight, age and environmental temperature (WHO, 1967).

Table 10. Recommended intakes of thiamine for adults of different body weights

	Bodyweight (kg)							
men	45	50	55	60	65	70	75	80
mg/day	1.0	1.1	1.1	1.2	1.3	1.4	1.4	1.5
women	35	40	45	50	55	60	65	70
mg/day	0.7	0.7	0.8	0.9	0.9	1.0	1.0	1.1

C *Physical activity*
The increase in energy requirements which accompanies increased physical activity leads to a corresponding increase in the absolute requirement of thiamine with no alteration in the thiamine to calorie ratio. A marked increase in physical activity is said to precipitate symptoms of thiamine deficiency in individuals subsisting on diets inadequate in thiamine. The joint FAO/WHO expert group (WHO, 1967), however, stated that there was no need to modify the recommended thiamine/calorie relationship in situations of heavy physical activity.

In non-deficient individuals over 50% of body thiamine is found in muscle. Anderson and others (1986) reported that sex differences in thiamine requirements and differences incurred during the adaptation processes accompanying sustained exercise programmes or starvation, could largely be explained by differences in total body mass.

C *Age*
Minimal requirements for dietary thiamine may increase with age, particularly for active individuals. The studies carried out by Oldham (1962) have shown that older women (over 50 years of age) have lower thiamine excretion at all levels of intake and have slower response to partial thiamine repletion compared to younger women. This would suggest that a higher thiamine-calorie ratio may be needed by older than by younger individuals.

• *Pathological conditions*
The joint FAO/WHO expert group (WHO, 1967) stated that it was not known whether conditions such as infections, gastrointestinal disease, thyroid disorders, trauma or chronic over-consumption of alcohol significantly modify the requirement for thiamine in relation to calories. Thiamine nutriture is said to be sufficient provided the recommended thiamine to calorie ratio is maintained.

However, it has also been reported that in abnormal physiological circumstances such as intravenous feeding, heavy alcoholism, liver disease, excessive carbohydrate intake, and use of powerful diuretics, clinical thiamine deficiency can develop despite daily administration of 1.24 mg or more of the vitamin (Anderson et al, 1986).

Hypervitaminosis/toxicity

Excess thiamine is cleared by the kidneys. There is some evidence of toxicity from large doses given parenterally. The dose that produced these reactions varied from 5–100 mg (F. Hoffman-LaRoche, 1994). Very rarely hypersensitivity reactions have also been reported after extremely high oral doses in the range of 5–10 g (F. Hoffman-LaRoche, 1994). However Hawk and others (1954) reported that oral doses of 500 mg taken daily for a month were found to be nontoxic.

Dosage of thiamine supplementation for preventing and treating thiamine deficiency

Treatment

Thiamine is specific in the treatment of beriberi and other conditions associated with thiamine deficiency. In mild deficiency states including lactating women at risk of inadequate thiamine intakes, a daily oral dose of 10 mg thiamine should be given during the first week, followed by 3–5 mg for at least six weeks. In severe deficiency states the following dosages are recommended:

- *infantile thiamine deficiency:*
  if severe heart failure, convulsions or coma occur, 25–50 mg of thiamine should be given very slowly intravenously, followed by a daily intramuscular dose of 10 mg for about a week. This should then be followed by 3-5 mg of thiamine per day orally for at least 6 weeks.

- *critically ill adults:*
  50–100 mg thiamine should be administered very slowly intravenously, followed by the same oral doses as for infants.

In infants with thiamine deficiency and in adults with cardiac insufficiency the response to treatment is dramatic, with symptomatic relief within hours, whereas deficiency states with peripheral neuritis show a less spectacular improvement. The ocular manifestations of Wernicke's syndrome improve promptly, within hours, with the administration of the large doses of thiamine, but the response of the Korsakoff's psychosis is slow and incomplete in the majority of patients (Feldman, 1988).

Prevention

Preventive therapy should be given to people with limited intake, malabsorption, or increased requirements lasting more than two weeks. Consumption of about 1 mg of thiamine daily is sufficient to prevent thiamine deficiency. When the staple cereal is polished rice or cassava, special efforts need to be made to include legumes and/or nuts in the ration.

Sources of thiamine

Distribution in foods

Thiamine is practically present in all plant and animal tissue, but most contain only low concentrations of the vitamin (see Table A, Annex 3). In plants, thiamine occurs predominantly as free thiamine and in animals almost entirely (95-98%) in phosphorylated forms, the predominant form being thiamine pyrophosphate (Combs,1992). The richest source of thiamine is yeast. Cereal grains, however, comprise the most important dietary source of the vitamin in most human diets. For example, even in the USA and the UK, cereals contribute 52% and 48% respectively of the total thiamine intake followed by meat products in the USA which provide 21% of the daily thiamine intakes (USDA, 1995); and by vegetables in the UK, which provide 18% of the daily thiamine intakes (Anderson et al, 1996).

Thiamine is very unevenly distributed in the kernel of whole grain; the aleuron layer and germ are much richer than the endosperm; the scutellum (the thin layer between the germ and the endosperm), constituting only 1.5% of the weight of the whole kernel, is richest of all and usually contains 50 - 60% of all the thiamine in the kernel. Therefore, milling to degerminate grain yields a product of substantially reduced thiamine content. In highly milled flour only about 70 % of the grain is included and the thiamine content of such a flour is about 0.13 mg/100 g as compared to flour of 80–85% extraction which contain 0.32 mg/100 g. Table 11 comprises the percentage of daily thiamine requirements obtained from bread made from 70% extract and 95% extract wheat flour.

Table 11. Bread as a source of thiamine

Type of bread	Percent of daily requirements supplied (RDA as 1.2 mg)
200 g of unenriched white bread (70% extract flour)	10
200 g of whole wheat bread (95% extract flour)	50

Source: Adapted from Marks (1975)

Rice, in the brown form, has a somewhat lower thiamine content; 0.33 mg/100 g, than the best whole wheat. In highly milled white rice only about 0.08 mg/100 g remains and this may be further reduced by half by washing the rice before cooking. Hand-pounded rice is rarely as white as machine-milled rice and its content of thiamine is 0.16 mg/100 g (FAO, 1964).

Pulses contain about 0.40–0.80 mg thiamine/100 g. In many areas where rice is the staple, they represent one of the most feasible options to provide for adequate thiamine intakes on polished rice diets. Fresh potatoes contain 0.10 mg of thiamine/100 g but since their water content is about 80%, this is equivalent to 0.35–0.40 mg of thiamine/100 g of air-dried matter. Cassava and other roots are less rich in thiamine and cassava flour does not even contain detectable amounts of thiamine.

Cow's milk contains about 0.04 mg of thiamine/100 g but as it is 87% water it is among the thiamine rich foods on a dry weight basis. Pasteurisation of milk destroys about 10% of the thiamine. Human milk contains on average **a** as much thiamine as cow's milk.

In conclusion, nearly all living tissues contain thiamine and some thiamine is therefore derived from almost all articles consumed as food. It is only with refined cereals ie. white flour, white rice, degerminated maize meal, cereal starches, cassava and sago, as well as in products made from them, that the thiamine content is too low to support human life.

Other sources of thiamine

Intestinal bacteria synthesise thiamine and there is evidence that the requirements of thiamine may be lowered to some extent on diets corresponding to the increase in synthesis by intestinal bacteria. Since the microbiological character of the intestinal flora is influenced by the composition of the diet, the vitamin requirements might change with the proportions of dietary carbohydrate, fat, and protein (Bhuvaneswaran and Sreenivasan, 1962).

It has been reported that allicin in garlic reacts with thiamine to form alithiamine which is more readily absorbed in the intestine, is more stable than thiamine and is not decomposed by thiaminase (Williams, 1961).

Fermentation increases some vitamin B levels (Uzogara et al,1990) and has been reported that a thiamine-deficient diet when supplemented with milk curds appears to increase the intestinal synthesis of thiamine as shown by an increase in urinary and faecal thiamine excretions (Bhuvaneswaran and Sreenivasan, 1962).

Thiamine in breast milk

The literature, particularly that over the last two or three decades, documents infant beriberi as the only serious form of malnutrition which occurs in breast-fed infants receiving adequate quantities of milk from thiamine-deficient mothers. The maternal diet has been shown to be the principal determinant of the amount of thiamine transferred from the mother to the breast milk (see Table 12).

In 1962, based on a study in Manila, Salcedo reported thiamine values ranging from 18.2 Fg to 212.1 Fg thiamine per litre breast milk from apparently healthy mothers; the average thiamine content being 96.5 Fg/litre breast milk. If it is assumed that the average daily milk intake of an exclusively breast-fed infant between 1-5 months of age is approximately 750 ml, the expected daily intake of thiamine would therefore have been 72.3 Fg or 0.072 mg per day which does not cover the minimum daily requirement of 0.17 mg/day necessary to prevent deficiency (National Research Council [US], 1989).

In the 1930s, substances such as methyl glyoxal were extracted from the breast milk of thiamine deficient women that were later identified as intermediate toxic products in the metabolism of carbohydrates as a result of their incomplete oxidation. It was reported that after ingestion of milk containing such intermediate products, the infant tries to get rid of them partly by excretion

Table 12. Thiamine content of diet and breast milk of lactating women in India

Range of thiamine intake (mg/day)	Mean thiamine intake (mg/day)	Mean thiamine content of milk (Fg/litre)
0.09–0.26	0.21 ± 0.01	115.1 ± 0.78
0.26–0.46	0.36 ± 0.02	115.9 ± 1.06
0.46–0.76	0.58 ± 0.01	131.6 ± 1.00
0.76–2.74	1.23 ± 0.29	158.6 ± 1.14

Source: Bhuvaneswaran and Sreenivasan, 1962

but mostly by further oxidation to their ultimate end products. For this purpose, thiamine, which is not sufficiently available, is absolutely essential. Due to lack of thiamine, the toxic products accumulate and cause infantile beriberi or breastmilk intoxication, as it was also called (Fehily,1941;1944).

Several studies were carried out to look at the thiamine contents of breastmilk in various groups of women (see Table 13). Valyasevi and others (1968) reported levels between 93 Fg/litre and 149 Fg/litre in Thailand. Comparative figures for thiamine content of breastmilk in India were reported as 153 Fg/litre and in the USA. as 142 Fg/litre. The average figure for the thiamine content of breastmilk as stated by Jelliffe and Jelliffe (1978) is 160 Fg/litre. A study carried out in 1980 by Nail and others (1980) looked at healthy, well-nourished, middle-class American women and came up with a figure of 138 Fg thiamine/litre breastmilk. They also reported a significant increase in the thiamine content of breastmilk in the first month of lactation. After 43 days of lactation the thiamine levels were 220 Fg/litre.

Table 13. Thiamine content of breastmilk in various groups of women

Groups of lactating women	Mean thiamine content of milk (Fg/litre)
India[a]	153
Thailand[a]	93–149
U.S.A.[a,b]	142, 138

[a] Valyasevi et al (1968); [b] Nail et al (1980)

Table 14 suggests guidelines for assessing breastmilk thiamine levels in lactating women. The assessment of the thiamine content of breastmilk together with the mortality figures of infants give valuable information on the existence of thiamine deficiency in a community.

Table 14. Proposed criteria for assessment of breastmilk thiamine levels

Thiamine status	Breastmilk thiamine (µg/l)
Normal range	100-200

Marginally deficient	50-99
Severely deficient	<50

Criteria drawn from: Salcedo J, Ann. N.Y. Ac. Sci. 1962, 98 Art. 2: 568-575; Concepcion I, Dee RL. Phil. J.Sci. 1949, 78: 373; NHMRC. Med. J.Aust. 1978, 1:232-235; Thanangkul O, Whitaker JA. Amer. J. Clin. Nutr. 1966, 18: 275-277; Valyasevi A, Vimoksant S, Dhanamitta S. J. Med. Ass. Thai. 1966 51, 348-353.

Factors influencing content and utilization of thiamine in foods

Stability in foods

Losses

Thiamine is water soluble and is susceptible to destruction by several factors including:

- neutral and alkaline conditions
- heat
- oxidising and reducing agents
- ionizing radiation

Thiamine is stable at low pH (pH under 7), but decomposes when heated particularly under non-acidic conditions. Protein-bound thiamine, as found in animal tissues, is more stable. Thiamine is stable when stored frozen; however, substantial losses occur during thawing.

Table B, Annex 3, shows examples of thiamine losses in food processing. Losses of thiamine during the commercial baking of white bread, which is between 15 to 20%, is partly due to the yeast fermentation which can convert thiamine to co-carboxylase which is less stable than thiamine (Berry Ottoway,1993). According to a study reported by Marks (1975), the loss in the crust was 30% and that in the rest 7%; rusks, baked twice, lost 40–50%.

Thiamine is very sensitive to sulphites and bisulphites, especially at a high pH. Consequently there are large losses of the vitamin in vegetables blanched with sulphite, and in meat products where sulphites and bisulphites are used as preservatives. Berry Ottoway (1993) reported a thiamine loss in cabbage of 45% in sulphite-treated blanching water compared with 15% in untreated water. Where the pH is low, such as in citrus fruit juices, thiamine losses are considerably less. The practice of adding sodium bicarbonate to peas or beans for retention of their colour in cooking or canning results in large losses of the vitamin due to the alkaline environment.

Thiamine is also decomposed both by oxidizing and reducing agents eg. in the presence of copper ions. A comprehensive study of heat processing in tin and glass containers showed significant losses of thiamine; 50% of thiamine was retained after processing and the levels reduced to between 15–40% after 12 months storage (Berry Ottoway,1993). Prolonged dehydration of fruits and vegetables resulted in a loss of 30–50% of thiamine (WHO, 1967).

Thiamine is also cleaved by residual chlorine in proportion to the rise in temperature, rise in pH and

concentration of residual chlorine. During the cooking process thiamine in rice is lost because of residual chlorine in the cooking water. The study undertaken by Yagi and Itokawa (1979) shows that there is a loss of 65% of thiamine in polished rice that has been washed and cooked in water containing 0.2 ppm chlorine compared to a loss of 45% of thiamine in polished rice washed and cooked with distilled water containing no chlorine. The thiamine content of raw polished rice is 1.09 +/- 0.03 Fg/g and about 45% thiamine losses are expected during the washing and cooking processes. Using chlorinated water to cook rice increases the losses of thiamine from the rice by 20%. These extra losses can make a difference in populations where the intake of thiamine is marginal.

One kilo of raw polished rice contains on average 1.1 mg thiamine and would provide the daily requirement of thiamine. If the rice is cooked it would however only contain about 0.6 mg thiamine, and if chlorinated water is used, the thiamine content of the cooked rice would only be 0.38 mg.

The lime treatment of maize, as practised in Mexico and Central America, causes considerable destruction of the thiamine present in maize, although this process improves the bioavailability of niacin (WHO, 1967).

Interaction with other micronutrients

The fortification and the enrichment of products using more than one added vitamin can increase the possibility of mutual interactions of the vitamins. Most of the work carried out in this area has tended to concentrate on both the stability and the solubility of the vitamins in aqueous multivitamin solutions. Thiamine has been shown to have a significant effect on the stability of folic acid, particularly in the pH range of 5.9 to 7. The decomposition of thiamine can also increase the breakdown of vitamin B_{12} (cyanocobalamin).

Vitamin C appears to play a protective role if it is consumed together with thiamine. In animal studies the addition of large amounts of vitamin C to a purified diet reduces the requirement for thiamine. Five percent vitamin C added to a thiamine-free diet prevented or delayed the onset of thiamine deficiency signs (Bhuvaneswaran and Sreenivasan, 1962). However, vitamin C supplementation of the diets of thiamine-deficient rats maintained normal ascorbic acid blood levels but was without effect on blood pyruvate levels.

Recommendations to reduce losses

Thiamine losses from cereals could be reduced drastically if flours of higher extraction rates are used, for instance, for baking bread. Rice would retain more thiamine if it were not highly milled. However, people usually prefer refined flours and polished rice; changing their preferences and food habits is known to be extremely difficult. Many countries have therefore opted to enrich or fortify refined products with the necessary vitamins.

Thiamine and other vitamins can be retained in rice by the process of *parboiling*, which is an old technology first used in India. Rice in the husk is soaked in water, steamed at atmospheric pressure for 20 to 30 minutes, dried in the sun and subsequently pounded or milled. The steaming splits the husk, making its separation easier, and this was probably the original purpose of parboiling. More importantly, steaming causes thiamine and other nutrients to migrate from the outer layers into the

endosperm, so that removing the outer layers by milling does not denude the grain of thiamine. Parboiling also has the effect of making the thiamine less accessible to water when rice is washed before cooking. Parboiled rice may be milled to a high degree and yet retain enough thiamine to prevent beriberi as evidenced by the absence of beriberi in areas in India where parboiled rice is generally consumed.

Other rice eating communities in South-East Asia have never adopted this method of processing rice and do not like the taste and consistency of parboiled rice. Williams (1961) has enumerated additional advantages of parboiling: (i) parboiled rice is not extensively attacked by weevils since the glazed surfaces are hard enough to resist the weevils' bite; (ii) the rice grows rancid more slowly than under-milled rice because its enzymes have been destroyed by the heat; (iii) due to the toughening of the rice grain the amount of breakage is reduced during subsequent milling. In the 1940s, a method based on parboiling was developed in the U.S.A. and parboiled rice was produced on a large scale.

The losses that occur during the preparation of food can also be minimized. Ideal food- preparation and cooking methods for the preservation of thiamine are as follows:

- Use the minimum amount of water for the preparation of vegetables and do not discard the cooking water.
- Cook for the minimum amount of time possible; a high temperature for a short time is preferable.
- Cover the pot with a lid to shorten cooking time.
- Storage of raw foods should be kept to the minimum possible and cooked foods should not be stored.
- Wash vegetables before cutting them.
- If possible rice should not be washed before cooking. If necessary, rinse once only with a little cold water.
- Do not cook rice with excess water that needs to be discarded.
- Use parboiled rice where available.

Nutrition education messages based on the above guidelines can contribute to keep losses of thiamine at a minimum. This can play an important role in situations where the intake of the vitamin is marginal and subclinical beriberi is prevalent.

Anti-thiamine factors

Thiamine in foods can be destroyed by anti-thiamine compounds that occur naturally in food or are produced in food as a result of microbial or other action. Dietary analyses may indicate adequate intakes of thiamine, but do not take into consideration the influence of anti-thiamine factors in the diet that may affect the requirement of the vitamin. Studies indicate that situations may exist where such factors may influence the availability of the thiamine present in the food.

An early documented case of thiamine deficiency resulting from the ingestion of food containing such thiamine antagonists was that seen on a fox farm owned by Mr. Chastak in the 1940's. The neurological disorder in the commercially raised foxes fed a diet containing about 10% raw carp was referred to as 'Chastak paralysis'. The condition was brought on by a thiamine-degrading enzyme (thiaminase) present in fish gut tissue. Cooking the fish prior to feeding them to the foxes prevented occurrence of the syndrome, apparently by heat-denaturation of the thiaminase. Thiaminases are

present in the raw tissues of many fishes, chiefly fresh water fishes but also in Atlantic herring. These are heat labile and can be effective antagonists of the vitamin when consumed without heat treatment (Combs, 1992).

In the Philippines, the Tagalog word for beriberi is 'bangungut' which means nightmare and classically death occurs in sleep after a heavy meal consisting of rice and fish (Lonsdale, 1990). The thiaminase in the fish may compound an initial marginal dietary thiamine deficiency and can be fatal.

Probably the first description of thiaminase poisoning in humans was documented in the diaries of explorers in 1860-61 in Australia (Steinhart et al,1995). An Australian fern (*Marsilea drummondii*) with high levels of thiaminase was the cause of the death of the explorers. Aboriginal people in Australia prepared the fern sporocarps by grinding them with water to make a flour paste which could then be made into bread or eaten in a soup. However, the expedition members failed to realize the importance of this method of preparation and did not leach out or inactivate the thiaminase in the fern before consumption. The expedition members became progressively weaker, developed muscle wasting and eventually died of beriberi.

Heat-stable thiamine antagonists occur in several plants; ferns, tea, betel nut. They include *polyphenols*; these and related compounds are found in blueberries, red currants, red beets, brussel sprouts, red cabbage, betel nuts, coffee and tea (Hilker and Somogyi, 1982). They react with thiamine to yield the non-absorbable thiamine disulfide. In addition, some *flavonoids* have been reported to antagonize thiamine as well as *haemin* in animal tissues. (See Table 15).

Some bacteria (e.g. *Bacillus thiamineolyticus*) are also capable of destroying thiamine. It has been reported that 3% of Japanese show a thiamine deficiency due to this cause. Thiaminase bacteria have been frequently isolated from human stools in Japan and it was reported that the thiamine levels in the blood of these patients was low in spite of adequate intake largely due to the destruction of thiamine in the intestines (Bhuvaneswaran and Sreenivasan, 1962).

In Thailand, biochemical thiamine deficiency was reported to be common in the northern and north eastern provinces. Approximately 25% of the subjects studied were found to be deficient, i.e. TPP effect > 20% (Vimokesant et al,1975) and showed signs of extremity numbness, anorexia, weakness and aching of calf muscles. In the northern provinces about 80% of the adults chewed fermented tea leaves as a stimulant while betel nut chewing was common in other areas. In the north eastern provinces, fermented fish was eaten daily. A study undertaken by Vimokesant and others (1975) showed that the abstention from both betel nut chewing and raw fermented fish consumption resulted in a significant reduction of the TPP effect. The TPP effect again increased significantly when the subjects resumed their chewing habits. Cooking of fermented fish

Table 15. Types of anti-thiamine factors and their actions

Anti-thiamine factor	Mechanism	Source
Thiaminase [1]		
Type I	alters the structure of thiamine	raw or fermented fish, shellfish, ferns, some bacteria
Type II	reduces biological activity of thiamine	certain bacteria
Thiamine antagonists [2]		
polyphenols (e.g. caffeic acid, chlorogenic acid, tannic acid)	interferes with absorption or digestion of thiamine	tea, coffee, betel nuts, red cabbage, blueberries, red currants, red beets , also in cereals, pulses, oilseeds
flavonoids (e.g. quercetin, rutin)	''	widely distributed in edible fruits and vegetables, buckwheat plants
haemin	''	animal tissues

[1] heat labile enzyme
[2] heat stable non-enzymatic factors

destroyed thiaminase and resulted in a significant decrease of the TPP effect. Thiamine supplementation (10 mg/day) further decreased the TPP effect and could counteract the effect of raw fermented fish consumption but was not sufficient to neutralize the effect of betel nut chewing. The habitual diet of the people studied provided for the RDA for thiamine (1.0 mg/day) thus suggesting that the regular consumption of natural anti-thiamine substances can lead to a biochemical thiamine deficiency even in the presence of adequate dietary thiamine intakes.

Another cause of thiamine deficiency in Thailand was reported to be tea drinking and chewing of fermented tea leaves ; tannins being the major component having anti-thiamine activity (Hilker et al,1971). A study by Kositawattanakul and colleagues (1977) found that ascorbic acid (vitamin C) protected the modification of thiamine by tea extract, not only at acidic pH, but also at neutral pH. High concentrations of Ca^{2+} and Mg^{2+} present in water were also reported by Vimokesant and others (1982) to augment the precipitation of thiamine by tannins. The precipitate formation makes thiamine less available for absorption by the intestine. Again, ascorbic acid, tartaric acid, and citric acid, all present in many vegetables and fruits, are said to lower such precipitation and increase thiamine bioavailability.

The following recommendations were made to decrease the influence of anti-thiamine factors in reducing thiamine absorption (Vimokesant et al, (1982):

- delay the consumption of tea or other tannin-containing products after a meal;
- consume foods high in ascorbic acid along with the meals;
- heat products containing thiaminase before consumption.

Strategies to prevent thiamine deficiency in large populations affected by emergencies

Background

In general, the most effective way to prevent micronutrient deficiencies, including thiamine deficiency, is to consume a diet containing a variety of foods, including fresh foods. Emergency food rations usually consist of a cereal staple, pulses and oil. If the staple distributed is polished rice, highly milled wheat flour, or cassava/tubers the thiamine content of the ration is very low. Populations depending entirely on such a limited range of foods run the risk of developing thiamine deficiency even if their energy intake is adequate. An analysis of 24-hour food intake surveys carried out among Karen refugees in Thailand where thiamine deficiency was encountered (MSF/Epicentre, 1992) showed that just over 2 000 kcal were consumed: 83% was carbohydrates, 11% proteins and 6% was fat. The main cereal consumed was polished rice and the daily thiamine intake was 0.75 mg which is below the minimum RDA of 1 mg.

Main approaches

The main approaches to preventing thiamine deficiency in emergency situations affecting large populations are as follows:

- Providing food rations containing adequate amounts of thiamine by increasing the variety of the food basket and regularly including adequate amounts of legumes and vegetables.
- Providing parboiled rice or undermilled rice or other undermilled cereals instead of polished rice or other highly milled cereals.
- Fortifying current relief commodities with thiamine, e.g. providing fortified blended cereal-legume food in the general ration in sufficient amounts to cover thiamine requirements.
- Providing sufficient food in the ration to allow refugees to trade for a more varied diet.
- Providing thiamine (vitamin B-complex) supplements in the form of tablets.

Several of these options have been tried in various refugee settings with varying degrees of success. The advantages and disadvantages of some approaches are discussed below.

Diversification of diet

Legumes (pulses, beans and groundnuts) are a good source of thiamine and should be part of the food basket of the affected population. Locally accepted types of legumes should be distributed to ensure that they are consumed. Lentils distributed in the ration were the most commonly exchanged items among the refugees in Nepal since the distributed lentils were not the customary type used by the refugees in their homeland (SCF(UK) report, 1994).

Vegetables are also a source of thiamine and of other micronutrients and where feasible should be distributed as part of the general ration.

As a longer term strategy, diversification should be promoted by supporting vegetable cultivation as a routine component of all emergency-affected population assistance programmes. Nutrition

education to promote the consumption of appropriate foods is an important component of any strategy.

Distribution of parboiled rice or undermilled rice in place of polished rice

The benefits of parboiled rice besides being a richer source of thiamine than polished rice have been mentioned earlier. In areas where rice is the staple food attempts should be made to introduce the parboiled variety. The organoleptic qualities of parboiled rice can vary greatly from polished white rice and a strong education programme is vital for the success of such an intervention. The experience in the Bhutanese refugee camp in Nepal showed that the quality control of parboiled rice was very important in order to ensure the distribution of a uniform quality of the rice.

Depending on the degree of milling, undermilled rice can have quite a high thiamine content. The main disadvantage of undermilled rice is the difficulty in keeping the quality of the product. The storage losses of thiamine in undermilled rice can be high. Undermilling also does not give the colour or cooking quality required by many consumers and it is very difficult to introduce it in areas where white polished rice is preferred.

Addition of thiamine-rich commodity to the food basket

When the general ration foods do not contain adequate natural sources of micronutrients, fortified legume-cereal blends have been added to the general ration of emergency-affected populations to cover their requirements for the various micronutrients. Research carried out by OXFAM/UNHCR (Mears and Young, 1998), looked at the usage of blended foods in an emergency at the household level. In addition to investigating refugee preferences for a range of ration and non-ration foods, this study looked at the feasibility of cereal fortification in a refugee situation. There were no major problems with either the use or acceptability of blended foods. The study, however, highlighted some technical and operational issues regarding quality control and timely supply of locally produced food products. The strategy of cereal fortification clearly involves major issues of technical and operational feasibility in Africa which need to be dealt with for successful implementation of the use of fortified blended cereal foods. The disadvantages of using a special food originally designed for the supplementary feeding of malnourished children, which include: costs, shortage of the item, dependency on non-local product, have been discussed by Beaton (1995), by the Refugee Policy Group (1997) and by others (Toole, 1992).

Corn-soya-blend (CSB) provided by manufacturers in the US and Europe contains approximately 0.6–0.8 mg of thiamine per 100 g. The inclusion of 60 g of CSB to the general ration would bring the thiamine content of the ration to 1.1 mg which would cover the RDA for thiamine (0.9 mg for a mixed population). However, field studies would have to look at the preparation and cooking losses which have not been calculated in the above figure. Currently not more than 30 g of cereal-legume blend per day is distributed in the ration which clearly does not provide for the daily requirement for thiamine if this is the only major source of the vitamin (see Table 2, for the thiamine content of a rice-based ration).

Biscuits are another food vehicle suitable for fortification with thiamine and have been distributed in several emergency-affected situations since they are ready to be consumed, need no preparation or cooking and are usually consumed by all members of the family.

Supplementation with thiamine/vitamin tablets

Regular thiamine or vitamin B-complex tablet supplementation is logistically difficult in large populations affected by emergencies. Thiamine or vitamin B-complex tablets need to be given daily; this is difficult to organize, expensive, and may be ineffective in the long term. Routine supplementation is recommended only as a means to treat outbreaks of the deficiency disease. However, vitamin B-complex tablets can be distributed to pregnant and lactating women via antenatal and postnatal clinics as a preventive measure.

Additional approaches

Reduction of losses of thiamine during preparation and cooking of meal

The losses of thiamine during the preparation and cooking of rice can be greatly reduced by:

- *Reduction of the number of washes of the rice before cooking*
  Most rice-eating communities wash the rice grains before cooking the rice. A survey carried out among refugees in Thailand reported that just over 75% of the cases surveyed washed the rice twice and over 12% washed the rice three times before cooking it (MSF/Epicentre, 1992). Washing the rice grains with large quantities of water leaches out a large percentage of the thiamine present.

- *Cooking of rice in two volumes of water only*
  Usually rice is cooked in a large quantity of water which is thrown away after the rice has been cooked. If rice is cooked in two volumes of water there is usually no water left after the cooking period. In any case the cooking water should not be discarded and can be used as a beverage and in the preparation of other foods.

The cooking losses of thiamine in vegetables can be reduced by:

- washing of vegetables before cutting them into small pieces;
- reducing cooking time to a minimum;
- immediate consumption of freshly prepared meal;
- cooking vegetables in minimum amount of water and consuming the water.

Reduction of the intake of anti-thiamine factors

Anti-thiamine factors are present in tea and in betel nuts and can have a direct influence on the development of thiamine deficiency especially in populations where thiamine intake is already marginal. Nutrition education and information campaigns are necessary to modify the food habits in such a population where the reduction of the intake of anti-thiamine factors can make a difference in the thiamine nutriture of the people.

Fortification of appropriate food item with thiamine

Staple foods poor in thiamine such as polished rice or milled cereals can be enriched with thiamine. The technology for the fortification of **milled rice** was developed in the USA in the 1940s. The

method consists of fortifying grains of ordinary, milled, white rice with a high concentration of the desired supplementary nutrients i.e. thiamine, to produce a premix. The premix is covered by a film-forming, water insoluble coating that easily disperses during cooking. The premix is added to the raw polished rice and cannot easily be distinguished once it is added. Technically this fortification process is viable and economically advantageous since only 1–2% of the rice requires special processing. However, rice fortified in this way has not been acceptable because of the washing losses which range from 10 to 20%. More recently a new premix method has been developed based on the manufacture of synthetic rice kernels incorporating micronutrients like thiamine. The rice kernel premix is added to normal white rice at the rate of e.g. 1 : 200 to provide the appropriate level of nutrients in the fortified rice. During cooking the nutrients are released from the premix kernels and are evenly distributed throughout the product. (WHO, 1976; USAID, 1993)

An alternative method for the fortification of milled rice developed in Japan was reported by Bhuvaneswaran and Sreenivasan (1962). It consisted of using dibenzoyl thiamine, a derivative of thiamine soluble only with difficulty in water but readily absorbed from the intestines and subsequently physiologically available to the body. The premix was known as 'vitarice' and was available at a cheap price in shops in Japan, and the premix was usually added to the milled rice at the household level.

Wheat flour is a suitable food vehicle for fortification with thiamine. Fortification of white flour with a premix containing thiamine in addition to niacin, riboflavin and iron is carried out in many developed countries. The stability of thiamine in the fortified flour was reported as being very good with only 5% of thiamine lost after a storage period of 6 months. Bread baked with fortified flour retains its thiamine activity (USAID, 1993).

Corn meal can also be successfully fortified with thiamine and trials have shown no loss of the vitamin after 6 months storage of the fortified meal.

From a technical stand point **salt** can also be fortified with thiamine but no trials have yet been undertaken to look at the cooking losses of thiamine in fortified salt.

Conclusions and recommendations

Populations affected by emergencies and dependent on food aid where milled rice is the major cereal distributed, and those dependent on starchy staple foods such as processed cassava and sago with few possibilities of diversifying their diets, usually have a low intake of thiamine even if their energy intake is adequate. A diet based on polished rice or any highly milled cereal, is high in carbohydrates which augments the thiamine requirement and is compounded by a low thiamine content. Thiamine deficiency can develop within 12 weeks of a deficient intake.

Although frank thiamine deficiency in non-emergency affected populations is rare today, large segments of the world's population continue to subsist on marginal or sub-marginal intakes of thiamine. People exposed to subclinical thiamine deficiency are predisposed to manifest frank beriberi under appropriate circumstances.

Nearly all living tissues contain thiamine and some thiamine is therefore derived from almost all foods. It is only with refined cereals i.e. white flour, white rice, degerminated maize meal, cereal

starches, cassava and sago, as well as in products made from them, that the thiamine content is too low to support human life. Thiamine losses from cereals could be reduced drastically if flours of higher extraction rates are used. Rice would retain more thiamine if it were not highly milled; or if it was parboiled before milling. However, thiamine is water soluble and susceptible to destruction by several factors including: heat; oxidizing and reducing agents; neutral and alkaline conditions. Losses that occur during the preparation of food can be minimized by improving preparation and cooking methods. In addition, thiamine in foods can be destroyed by anti-thiamine compounds that occur in foods.

It is difficult to speak of specific clinical symptoms of thiamine deficiency because of the variations of the clinical signs brought about by the presence of complicating factors, such as infections, or by the presence of symptoms from multiple deficiencies such as other B vitamins, vitamin C and minerals as well as the effects of stresses, such as physical labour and pregnancy. The clinical picture of frank thiamine deficiency in adults is, however, usually divided into a dry (neuritic) type and a wet (cardiac) type. The disease manifests itself principally with changes involving the nervous system, the cardiovascular system, and also the gastrointestinal tract. If untreated thiamine deficiency leads to death. Thiamine deficiency in infants (infantile beriberi) is an acute disease that mainly affects infants breast-fed by women having deficient thiamine levels. The onset of the symptoms is often very rapid and the fatality rate is very high. Infantile beriberi must be suspected in a population if there is a high incidence of death in the first five months of life, particularly months 2-4.

Even a single case of clinical thiamine deficiency seen in a population reflects a public health problem and calls for a full nutritional assessment using biochemical methods to assess the thiamine deficiency where feasible.

Not all interventions to prevent thiamine deficiency are feasible in every emergency setting. The principle way of addressing thiamine deficiency is by improving the diet. Securing an adequate diet for large emergency-affected populations where polished rice is the staple can be a problem especially in the initial phase of a relief operation. Distribution of parboiled rice where it is accepted would be one of the ways to help address the problem. Table 16 summarizes several of the options for interventions to prevent or control thiamine deficiency during an emergency.

Primary strategies

The following approaches need to be considered to improve the thiamine content of a ration where natural sources of thiamine are available:

- Provision of adequate quantity of legumes (pulses) and vegetables. Legumes represent one of the most feasible options to provide for adequate thiamine intakes where polished rice is the staple. Fresh vegetables are also a source of thiamine and of other micronutrients and should be distributed as part of the general ration where feasible, if not readily home-grown.

Table 16. Options for the prevention of thiamine deficiency in an emergency

A. Natural sources of thiamine available locally

Natural sources available immediately

1. Provide adequate amounts of legumes and vegetables
2. Provide parboiled rice or lightly milled rice instead of polished rice
3. Provide lightly milled cereals (wheat, maize)
4. Encourage barter or purchase by providing 10% extra ration

Natural sources not available immediately

5. Encourage household food production of legumes, coarse grains (maize, millet), vegetables by providing necessary inputs

B. Natural sources not available locally

Provision of commodities fortified with thiamine

3. Provide fortified cereal-legume blends in the general ration
4. Provide fortified cereals in the general ration

Provision of thiamine supplements

5. Provide thiamine (vitamin B-complex) supplements

- Provision of parboiled rice instead of polished rice. Parboiled rice is a richer source of thiamine than polished rice and in areas where rice is the staple food attempts should be made to introduce the parboiled variety.
- Provision of lightly milled cereals (rice, wheat, maize) instead of highly milled ones. Lightly milled cereals are good sources of thiamine and should therefore be distributed where feasible, i.e. where availability, acceptance and storage problems can be overcome.
- Provision of extra quantity of ration to encourage barter and/or purchase. Sale and/or barter of a portion of the ration should be encouraged where markets are available to enable the emergency-affected population to diversify their diet and thereby help cover their micronutrient needs.

The following approach of distributing fortified commodities needs to be considered to support the other interventions or as an alternative if the other interventions are not feasible:

- Provision of fortified cereal-legume blends. The inclusion of 60 g of CSB to the general ration would cover the requirements for thiamine without considering preparation and cooking losses.
- Provision of fortified cereals. Milled rice, wheat flour and corn meal can be fortified with thiamine. However, the logistics and feasibility of cereal fortification at distribution sites and

the retention of the vitamin during storage, distribution and meal-preparation needs to be assessed.

In situations where a population is at high risk of thiamine deficiency or where cases of thiamine deficiency have already been identified and all the other options for intervention are not immediately feasible, the following alternative needs to be considered:

- Supplementation with thiamine (vitamin B-complex) tablets. Routine daily supplementation is only recommended as a means to treat outbreaks of the deficiency disease. However, as a preventive measure vitamin B-complex tablets can be distributed to pregnant and lactating women via antenatal and postnatal clinics.

The interventions to prevent thiamine deficiency have to be adapted to the phase of an emergency feeding operation into short-term and longer-term solutions. The initiation phase may involve fortified food aid commodities, parboiled rice, or possibly locally procured legumes, vegetables and coarse grains, or where feasible an increase of the general ration by 10%. Promotion of home gardens as well as promotion of local trading and, where feasible, local milling to produce lightly milled cereals may be options during the establishment phase of an operation. Longer-term solutions to prevent thiamine deficiency should always aim at the self-sufficiency of emergency-affected households which includes local production of vegetables as well as local trading.

Supporting strategies

- ***Nutrition education***. Nutrition education should be seen as an essential component of any intervention to prevent thiamine deficiency. Information, education and communication programmes that convey important messages can be inexpensive and achieve impact. The most efficient and durable interventions involve communication to educate and thereby modify consumption-related attitudes and practices. Messages to refugees can be vital in helping them to learn about their new environment, about different local foods that could be produced or purchased, and help in introducing unfamiliar imported food aid. Messages on how to reduce losses of thiamine during preparation and cooking of e.g. rice (see section 'Reduction of losses of thiamine during preparation and cooking of meal') could help in preventing thiamine deficiency. Nutrition education and information campaigns on the disadvantages of the intake of thiaminase and thiamine antagonists (e.g. raw fish, betel nuts, tea, coffee) would help to modify the food habits in a population where the reduction of the intake of anti-thiamine factors could make a difference in the thiamine status of the people.

- ***Training of field workers***. Improving the skills of field workers in the clinical assessment and management of thiamine deficiency through training is essential for an intervention to be effective. It is also necessary to develop their capacity to analyze options and take appropriate action for the prevention of thiamine deficiency in emergency-affected populations where there is a likelihood of an outbreak or risk of thiamine deficiency.

- ***Establishment or identification of facility for biochemical assessment of thiamine deficiency***. Currently there are no field-friendly methods available for the biochemical assessment of thiamine deficiency. It is therefore necessary to identify facilities at the national level, or in a neighbouring country, where the thiamine status can be determined rapidly and

with precision. Methods for the biochemical assessment of thiamine deficiency are summarized in the section 'Biochemical detection of thiamine deficiency'.

References

Alvarex OM, Gilbreath RL. Thiamine influence on collagen during the granulation of skin wounds. *Journal of Surgical Research,* 1982, 32:24-31.

American Academy of Pediatrics. Composition of human milk: normative data. In: *Pediatric Nutrition Handbook*, 2nd ed. Elk Grove Village, Illinois, 1985: 363-368.

Anderson SH, Vickery CA, Nicol AD. Adult thiamine requirements and the continuing need to fortify processed cereals. *The Lancet,* 1986, 2:85-89.

Anderson SH, Charles TJ, Nicol AD. Thiamine deficiency at a district general hospital: report of five cases. *Quarterly Journal of Medicine,* 1985, 55:15-32.

Australian Health and Medical Research Council. The thiamine status of Australian people. NH & MRC Report. *The Medical Journal of Australia,* 1978, 1:232.

Aykroyd WR. Nutritional problems of urban communities. *Proceedings of the Nutrition Society,* 1970, 29:148-50.

Barrett HR, Browne AW. Beri-beri: age-gender bias in The Gambia. *Social Science and Medicine,* 1992, 34:1295-1297.

Beaton GH. *Fortification of foods for refugee feeding* [Final Report]. Ottawa, Canadian International Development Agency, 1995.

Berry-Koch A et al. Alleviation of nutritional deficiency diseases in refugees. *Food & Nutrition Bulletin,* 1990, 12(2):106-112.

Berry Ottaway P. Stability of vitamins in food. In: Berry Ottaway P., ed. *The technology of vitamins in food*. Glasgow, Blackie Academic, 1993:90-113.

Bhuvaneswaran C, Sreenivasan A. Problems of thiamine deficiency states and their amelioration. *Annals of the New York Academy of Sciences*, 1962, 98:576-601.

Brin M, Ziporin ZZ. Evaluation of thiamine adequacy in adult humans. *Journal of Nutrition*, 1965, 86:319-324.

Brin M. Thiamine deficiency and erythrocyte metabolism. *American Journal of Clinical Nutrition*, 1963, 12:107-116.

Burgess RC. Beriberi. *Federation Proceedings*, 1958, 17 (Suppl. 2):3-56.

Campbell CH. Lacticacidosis and thiamine deficiency [letter]. *The Lancet*, 1984, 2: 1282.

Carney MW. Beri-beri in Blackpool. *British Medical Journal*, 1971, 2:109-110.

Clugston G. *A review of nutrition and food situation amongst the Butanese refugee camp populations* [Internal Report]. UNHCR, 1994.

Combs Jr GF. *The vitamins: fundamental aspects in nutrition and health.* San Diego, California, Academic Press, 1992.

Dahlberg K. Medical care of Cambodian refugees. *Journal of the American Medical Association*, 1980, 243:1062-1065.

FAO. Chatfield C. *Food Composition Tables (minerals and vitamins) for international use*. [Report]. Rome, Food and Agriculture Organisation of the United Nations, 1964.

Fehily L. Human-milk intoxication due to B1 avitaminosis. *British Medical Journal,* 1944, 2:590-592.

Fehily L. Does infantile beriberi occur in infants who have never been breast-fed? *The Transactions of the Royal Society of Tropical Medicine & Hygiene,* 1941, 35:177-182.

Feldman EB. *Essentials of clinical nutrition*. Essentials of medical education series. Philadelphia, F.A. Davis Company, 1988.

Feldman EB. Does nutrition play a role in cardiovascular disease? *Geriatrics*, 1980, 35:65-75.

Foltz EE, Barborka CJ, Ivy AC. *Gastroenterology*, 1944, 2:323.

Hawk PB, Oser BL, Summerson WH. *Practical physiological chemistry*, 13th ed. New York, McGraw-Hill, 1954.

Hilker DM, Somogyi JC. Antithiamines of plant origin: their chemical nature and mode of action. [Review]. *Annals of the New York Academy of Sciences*, 1982, 378:137-144.

Hilker et al. Antithiamine effects of tea: temperature and pH dependence. *Nutrition Reports International*, 1971, 4: 223.

F. Hoffman-LaRoche. *Vitamins (Basics)*, 1st ed. New York, Seaboard Lithographers, 1994.

Jeffrey HE et al. Thiamine deficiency - a neglected problem of infants and mothers - possible relationships to sudden infant death syndrome. *Australian & New Zealand Journal of Obstetrics & Gynaecology*, 1985, 25:198-202.

Jelliffe DB, Jelliffe EF. The volume and composition of human milk in poorly nourished communities. [A Review]. *American Journal of Clinical Nutrition*, 1978, 31:492-515.

Jukes TH. The prevention and conquest of scurvy, beri-beri, and pellagra. *Preventive Medicine*, 1989, 18:877-883.

Kawai C et al. Reappearance of beriberi heart disease in Japan. A study of 23 cases. *American Journal of Medicine*, 1980, 69: 383-386.

Kositawattanakul T et al. Chemical interactions between thiamine and tannic acid. II. Separation of products. *American Journal of Clinical Nutrition*, 1977, 30: 1686-91.

Lee YK. The Beri-beri Hospital, Singapore (1907-1925). *Singapore Medical Journal*, 1994, 35:306-311.

Lonsdale D. Thiamine deficiency and sudden deaths [letter; comment]. *The Lancet*,1990, 336:376.

Lonsdale D, Shamberger RJ. Red cell transketolase as an indicator of nutritional deficiency. *American Journal of Clinical Nutrition*, 1980, 33:205-211.

Macpherson C. The first recognition of beri-beri in Canada. *Canadian Medical Association Journal*, 1966, 95:278-279.

Marks J. *A guide to the vitamins: their role in health and disease*. Lancaster, UK, Medical & Technical Publishing Co. Ltd., 1975.

Marsden PD, Harling DS. Seasonal oedema in Gambian policemen. *Western African Medical Journal*, 1967, 16:13-19.

Mears C, Young H. *Acceptability and use of cereal-based foods in refugee camps - Case studies from Nepal, Ethiopia and Tanzania* (Oxfam Working Paper). London, Oxfam, 1998.

MSF/Epicentre. Study of the food habits of breast-feeding women among the Karen refugee population in the Mae Sod region, Thailand 1992, *Medical News*, 1992, 1:4.

Nagy K. *The role of food fortification in combating micronutrient deficiencies*. Basle, F. Hoffman-La Roche Ltd., 1996.

Nail PA, Thomas MR, Eakin R. The effect of thiamine and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *American Journal of Clinical Nutrition*, 1980, 33:198-204.

Neumann CG et al. Biochemical evidence of thiamine deficiency in young Ghanian children. *American Journal of Clinical Nutrition*, 1979, 32:99-104.

National Research Council [US]. *Recommended Dietary Allowances*, 10th ed. Washington D.C., National Academy Press, 1989.

Older MWJ, Dickerson JWT. Thiamine and the elderly orthopaedic patient. *Age-Aging*; 1982, 11:101-107.

Oldham HG. Thiamine requirements of women. *Annals of the New York Academy of Sciences*, 1962, 98:542-549.

O'Shea HE, Elsom KO, Higbe RV. Studies of B vitamins in human subject; mental changes in experimental deficiency. *American Journal of Medical Science*, 1942, 203:388-397.

Pongpanich B et al. Biochemical detection of thiamine deficiency in infants and children in Thailand. *American Journal of Clinical Nutrition*, 1974, 27:1399-1402.

Rolfe M et al. Urban beri-beri in The Gambia, West Africa. *The Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, 87:114-115.

Refugee Policy Group. *Approaches to the micronutrient fortification of food for displaced populations in Africa* (unpublished), 1997.

Reuter H, Gassmann B, Erhardt V. [Contribution to the question of the human thiamine requirement]. *Internationale Zeitschrift für Vitaminforschung*, 1967, 37:315-328.

Sauberlich HE, Skala JH, Dowdy RP. *Laboratory tests for the assessment of nutritional status*. Cleveland, CRC Press, 1974.

Sauberlich HE. Biochemical alterations in thiamine deficiency - their interpretation. *American Journal of Clinical Nutrition*, 1967, 20:528-546.

SCF (UK). *Report on the outbreak of suspected thiamine deficiency*. Jhapa, Nepal, Bhutanese Refugee Health Project. Save the Children Fund (UK), 1994.

Sebrell Jr WH. A clinical evaluation of thiamine deficiency. *Annals of the New York Academy of Sciences*, 1962, 98:563-567.

Sebrell Jr WH. Vitamins and public health. *Internationale Zeitschrift für Vitaminforschung*, 1952, 23:380-392.

Steinhart CE, Ellin Doyle M, Cochrane BA. *Food Safety 1995*. New York, Marcel Dekker, Inc. 1995.

Tang CM et al. Outbreak of beri-beri in The Gambia. *The Lancet*, 1989, 2:206-207.

Thanangkul O, Whitaker JA. Childhood thiamine deficiency in northern Thailand. *American Journal of Clinical Nutrition*, 1966, 18:275-277.

Toole MJ. *Preventing micronutrient deficiency disease*. Workshop on the improvement of the nutrition of refugees and displaced people in Africa. Machakos, Kenya, 1994.

Toole MJ. Micronutrient deficiencies in refugees. *The Lancet*, 1992, 339:1214 - 1217.

USAID/FHA/Food for Peace. *Supplement on emergency rations. Commodities Reference Guide* [draft]. 1993.

USDA. Haytowitz DB. Information from USDA's Nutrient Data Bank. *The Journal of Nutrition*, 1995, 125:1952-1955.

Uzogara SG, Morton ID, Daniel JW. Changes in some antinutrients of cowpeas (Vigna unguiculata) processed with 'kanwa' alkaline salt. *Plant Foods for Human Nutrition*, 1990, 40:249-258.

Valyasevi A, Vimokesant S. Chemical composition of breast milk in different locations of Thailand. *Journal of the Medical Association of Thailand*, 1968, 51:348-353.

Vimokesant S et al. Beriberi caused by antithiamine factors in food and its

prevention. [Review] *Annals of the New York Academy of Sciences,* 1982, 378: 123-136.

Vimokesant SL et al. Effects of betel nut and fermented fish on the thiamine status of northeastern Thais. *American Journal of Clinical Nutrition,* 1975, 28:1458-1463.

WHO. *Polyneuropathy in Cuba*. Press Release. Geneva, World Health Organization, September, 1993.

WHO. *Diet, nutrition and the prevention of chronic diseases*. Geneva, World Health Organisation, 1991. (WHO Technical Report Series No. 797).

WHO. Beriberi. In: *Nutrition in preventive medicine. The major deficiency syndromes, epidemiology and approaches to control.* Geneva, World Health Organisation, 1976 (WHO Monograph Series 62:136-145).

WHO. *Nutrition in preventive medicine. The major deficiency syndromes, epidemiology and approaches to control*. Geneva, World Health Organization, 1976. (WHO Monograph Series No. 62).

WHO. *Handbook on human nutritional requirements*. Geneva, World Health Organisation, 1974. (WHO Monograph Series No. 61).

WHO. *Requirements of vitamin A, thiamine, riboflavine and niacin. Report of a Joint FAO/WHO Expert Group.* Geneva, World Health Organization, 1967. (WHO Technical Report Series, No. 362).

Williams RR. *Toward the conquest of beriberi*. Cambridge, Massachusets, Harvard University Press, 1961.

Wood B, Breen KJ. Clinical thiamine deficiency in Australia: the size of the problem and approaches to prevention. *The Medical Journal of Australia*, 1980, 1:461-462.

Yagi N, Itokawa Y. Cleavage of thiamine by chlorine in tap water. *Journal of Nutritional Sciences and Vitaminology,* 1979, 25:281-287.

Annex 1

Summary of major symptoms of thiamine deficiency in adults, adolescents and older children

Wet beriberi:

- oedema
- hyperdynamic circulation and a large heart
  - restlessness
  - collapsing pulse indicative of increased systolic pressure and decreased diastolic pressure
  - jugular venous pulse (vein pulse in the neck) raised with pronounced pulse waves
  - systolic 'flow' murmurs and a third heart sound giving a 'galloping' rhythm that is accentuated when the patient lies on the left side and breathes in
- lungs usually clear
- no cyanosis

Hyperdynamic circulation can also be caused by severe anaemia; thyrotoxicosis; pregnancy; chronic liver disease; worm infestation; arteriovenous fistulae (a rare arterial malformation). Oedema can also be present in adult kwashiokor; nephritis; nephrotic syndrome; and intoxication (heavy metals, ethylene glycol, etc).

Shoshin beriberi:

- breathless
- wet crackles in low lung fields
- classical heart failure

Easily confused with other causes of heart failure

Dry beriberi:

- peripheral neuritis
- paraesthesia of the feet, diminished touch sensation
- joint position, vibration and pain sensation usually normal
- ankle and knee reflexes lost
- muscle weakness starting with feet

Korsakoff's psychosis:

- profound loss of recent memory, with preservation of past memory and an active imagination.

Wernicke's encephalopathy:

- irritable and forgetful progessing to characteristics of damage to mamillary bodies on base of brain which include:
  - ptosis (drooping of eyelids) and opthalmoplegia (squinting where the eye does not move outwards)
  - nystagmus (horizontal flickering of the eyes)
- other cranial nerve lesions leading to:
  - cerebellar ataxia (unsteadiness of hand and foot movements)
  - confusion and delirium before death

Easily confused with other forms of encephalopathy such as viral illness, cerebral malaria, sleeping sickness, etc.

Adapted from: Golden M, Diagnosing Beriberi in Emergency Situations. Field exchange. Emergency Nutrition Network. May 1997. Issue 1.

Annex 2

Summary of major symptoms of thiamine deficiency in infants

Infantile acute cardiac beriberi:

- peak prevalence in breastfed babies of 1-3 months of age
- colic, restlessness, anorexia, vomiting
- oedema, cyanosis and breathlessness with signs of heart failure leading to death
  - A increased pulse rate
  - A enlargement of the heart
  - A additional heart sounds
  - A a systolic murmur
  - A pulmonary oedema
  - A liver enlargement and low urine volume

Easily confused with: typhoid, malaria, pneumonia and septicaemia

Aphonic beriberi:

- peak prevalence in 4-6 month old infants
- initially hoarse cry until no sound is produced while crying
- restlessness, oedema, breathlessness and death

Infantile encephalitic beriberi ('pseudomeningeal' beriberi)

- peak prevalence in 7-9 months old infant
- nystagmus
- muscle twitching
- a bulging fontanelle
- convulsions and unconsciousness

Easily confused with: all forms of encephalitis and meningitis, malaria and acute vitamin A intoxication.

Adapted from: Golden M, Diagnosing Beriberi in Emergency Situations. Field exchange. Emergency Nutrition Network. May 1997. Issue 1.

Annex 3

Tables

Table A: Average thiamine content of some foods
Table B: Thiamine losses in food processing
Table C:: Studies on experimental thiamine deficiency in humans showing intakes of thiamine with the corresponding urinary excretion rate and clinical signs

Table A. Average thiamine content of some foods

	thiamine (mg/100 g)		thiamine (mg/100 g)
cereal		**fruits**	
wheat:		apples	0.04
whole grain	0.41	apricots	0.04
(85%) med.extr.	0.32	bananas	0.05
white flour	0.13	breadfruit	0.09
rice, brown	0.33	figs	0.04
rice, polished	0.08	grapes	0.06
rice *parboiled*	0.22	lemons	0.04
cornmeal	0.18	mangoes	0.05
oatmeal	0.63	oranges	0.08
sorghum	0.15	pears	0.02
pasta	0.13	pineapples	0.08
Pulses, nuts and seeds		**tubers/starchy roots**	
beans	0.46–0.63	cassava:	
chickpeas	0.40	fresh	0.06
groundnuts (unroasted)	0.84	meal/flour	0
lentils	0.50	potato	0.10
peas	0.72	sweet potato	0.10
soybeans:		yam	0.09
dry whole seeds	1.03	sago, raw	trace
flour full fat	0.77		
vegetables		**meats**	
broccoli	0.10	beef (thin)	0.07
cabbage	0.06	liver, pork	0.43
carrots	0.06	pork (medium)	0.42
cassava leaves	0.16	poultry	0.10
cauliflower	0.11	trout	0.09
peppers	0.07	veal	0.13
tomatoes	0.06		
spinach	0.11		
other		**dairy products**	
brewer's yeast	15.6	cheese	0.02–0.06
human milk	0.01	milk	0.04
eggs	0.12		

Source: FAO 1964. Food Composition Tables (minerals and vitamins) for international use.

Table B. Thiamine losses in food processing

Food item	Procedure	Percent Loss
wheat	milling (70% extraction)	70
bread	baking, commercial	15–20
milk	pasteurization	< 10
milk	sterilisation	20
milk	canning	30–50
meats	convection cooking	25–85
vegetables	heating with water	0–60
vegetables	blanching (brief exposure to boiling water or steam)	2–30
fruits, vegetables	room temperature storage	0–20
fruits, vegetables	dehydration	30–50

Sources: Combs (1992); WHO (1967), Berry Ottoway (1993);

Table C. Studies on experimental thiamine deficiency in humans showing intakes of thiamine with the corresponding urinary excretion rate and clinical signs

Subjects (number)	Thiamine intake (mg/1000kcal)	Daily urinary excretion (ug)	Clinical signs/ remarks	Reference
3 (healthy young women)	0.35	56–60	Minimum requirement.	(1) O'Shea et al1942
4 (healthy young men)	0.33–0.38	40–100	Decrease in appetite and decrease in endurance.	(2) Foltz et al 1944;
4 (healthy young men)	0.17–0.21 (for 4 weeks)	5–20	Muscular weakness+pains fatigue, loss of appetite.	(2) Foltz et al 1944;
6 (obese women)	0.4	24	Minimum requirement.	(3) Reuter et al 1967;
11 (patients in mental hospital)	0.22 (for 8 weeks)	15–30	Depression, irritable, nausea,vomiting	(4) Williams, 1961
11 (patients in mental hospital)	0.5	-	Symptom free.	(4) Williams, 1961
4 (healthy young men)	0.185 (3 months)	50 (average)	No objective symptoms.	(4) Williams, 1961