BERIBERI IN LOW INCOME GROUPS

A CLINICAL AND EXPERIMENTAL STUDY IN SURABAYA AND SURROUNDINGS

DJOENAIDI WIDJAJA

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A clinical and experimental study in Surabaya and surroundings

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DJOENAIDI WIDJAJA
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THESIS

in the **MEDICAL SCIENCES**

to obtain the Ph.D. degree
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by

DJOENAIDI WIDJAJA
born in Sumenep, Madura, Indonesia

The studies reported in this thesis were performed in the Dr. Soetomo Hospital Surabaya, Department of Neurology (head: Prof.Dr.B.Chandra).

In honour of
my late father
Elyas Widjaja

Dedicated to:
my mother,
Juliati;
our son,
Andi;
our daughters,
Kumala,
Lily,
Biati;
and especially to my wife,
Trifosa Indrawati,
for her unfailing and
courageous optimism that
this effort would find reward;
for her patience
with delayed meals
and postponed vacations;
for her affection
without which life would
be pale and drab

CONTENTS

CHAPTER 1

INTRODUCTION

Low income groups usually have a qualitatively inadequate diet, in combination with an inadequate energy intake. Factors which enhance the need for nutrients, such as heavy physical work, infection, pregnancy, lactation, and growth may provoke the development of nutritional polyneuropathy.
In many countries, rice is a staple food. Whereas in the past the rice was husked manually, nowadays this is done by rice milling machines. During the milling process, rice loses much of its original thiamine content. Additional treatment of the rice, such as washing and cooking, further reduces its thiamine content. In countries like Indonesia, where milled rice makes up more than 80% of the total intake of calories in the diet of low income groups, these groups are at great risk of developing thiamine deficiency, resulting in beriberi. The presence of antithiamines in certain fishes, tea, coffee, fruits, vegetables, etc. enhances this risk. Since an individual's thiamine requirement mainly depends on non-fat calories in the diet, consumption of diets predominantly carbohydrate in nature and deficient in thiamine predisposes people to thiamine deficiency.

The author, working in the Department of Neurology of the Dr Soetomo Hospital, Surabaya, noticed an increasing trend towards neuropathy in the years 1981 to 1989, which could not be attributed to diabetes mellitus, uremia, leprosy, Guillain Barré syndrome, or toxic neuropathy.
The tentative diagnosis of thiamine deficiency was made.
One of the objectives of this study is to prove the nutritional cause of the observed polyneuropathy.
To this end, an investigation has been carried out to assess the probable relationship between diet and neuropathy, notably thiamine deficiency.

Clinical neurophysiological examination studies were performed in order to confirm the clinical diagnosis of polyneuropathy in patients and to obtain definite proof in experimental studies with chickens. We also did experimental studies with chickens in order to proof the thiamine deficiency, since they also developed polyneuropathy in the same way as in human beings. The results of these measurements were to provide a better insight into the underlying pathological processes.
Electroneuromyographic examination may be a useful tool where neurological examination provided insufficient information, such as in infants and young children, and in cases of subclinical neuropathy.

CHAPTER 2

OBJECTIVES

1. To assess the incidence of (nutritional) polyneuropathy in income groups and over time.

2. To assess whether this neuropathy can be attributed to thiamine deficiency.

3. To assess the neurophysiological findings in neuropathy as observed in Surabaya, East Java, Indonesia.

CHAPTER 3

LITERATURE REVIEW

3.1 THIAMINE

3.1.1 History (Williams, 1961; Wuest, 1962)

Eijkman (1890), a Dutch medical officer at Weltevreden, Java, was the first to demonstrate in a dramatic experiment, that polyneuritis gallinarum can be induced in domestic fowls. The disease can be prevented by feeding them undermilled or home pounded rice. Eijkman mentioned that this disease had been known to occur spontaneously in chickens, pigeons and chicks in the East Indies.

Grijns (1896, 1911) found that any food, including meat, lost its "protective factor" when autoclaved at 110°-120°C. He attempted to isolate this substance, but although he got some highly active concentrates, they were not pure. His studies provided additional evidence of dietary deficiency as a cause of polyneuritis and beriberi.

Funk, a Polish chemist, extracted a crystalline substance from rice polishings. In 1911 he coined the word "vitamine" for it, meaning an amine essential for life The crystal of Funk turned out to have no antineuritic activity. Later "deficiency-preventing compound" was found without any "amine" group, even without any nitrogen. So the word vitamine was changed into vitamin

Jansen and Donath (1926) , two Dutch chemists, extracted rice polish in acid solution, adsorbed the active principle to activated Fuller's earth, eluted the adsorbate in the presence of dilute acid, and obtained about 200 mg of crystal. This vitamin-hydrochloride turned out to have antineuritic activity, which was tested by Jansen/Donath and Eijkman, respectively.

Jansen and Donath had, however, overlooked the presence of sulfur in the analysis of the crystal. Windaus et al. in Göttingen (1932) were able to isolate the antineuritic vitamin from yeast, and found to their surprise the sulfur content.

Williams (1936), born in Nellore, India, as the son of American missionaries, was the first to synthetize thiamine, after many years of endeavor and struggle. He worked together with J.K.Cline on the synthesis of vitamin B1.

3.1.2 Food sources

Lean pork, fresh and cured, and wheat germ are outstanding sources of thiamine. Liver and all organ meats, liver sausage, lean meats, poultry, egg yolk, fish, dry beans, peas, soy beans, peanuts, whole grain, enriched bread and cereals are excellent sources. Milk and milk products, fruit and vegetables are not rich in thiamine (Krause and Mahan, 1984).

3.1.3 Thiamine requirements and allowances

Thiamine is essential for the utilization of carbohydrates in the body and requirements are hence related to carbohydrate intake. Although there is some evidence of a "thiamine sparing" effect of dietary fat, it is not of such a magnitude that allowances have to be made for the sources of dietary energy. It has been

customary to express thiamine requirements in terms of mg per 1000 kilo-calories (kcal). Most studies show that beriberi occurs when the dietary intake is less than 0 30 mg/1000 kcal. As thiamine cannot be stored in the body, excess is excreted in the urine. Most people do so when dietary intake of thiamine is 0.33 mg/1000 kcal or more; therefore this amount may be considered the minimum need. To cover individual variation in this requirement, the Food and Agricultural Organization (FAO) and World Health Organization (WHO) (1967) have recommended a daily intake of 0.40 mg/1000 kcal. This amount has been used to calculate the recommended daily allowances for various population groups (Table 2.1). These allowances are lower than those formulated by the United States Food and Nutrition Board, National Research Council (revised 1980).

TABLE 2.1 RECOMMENDED DAILY ALLOWANCES FOR THIAMINE

years	mg/day for children	
0 - 1	0.3	
1 - 3	0.5	
4 - 6	0.7	
7 - 9	0.9	
years	**mg/day for males**	**mg/day for females**
10-12	1.0	0.9
13-15	1.2	1.0
16-19	1.2	0.9
20 +	1.2	0.9
		Pregnant + 0.1
		Lactating + 0.2

From the Food and Agricultural Organization (FAO) and World Health Organization (WHO) expert committee WHO Tech Rep Ser, No 362, 1967

A thiamine intake of 1.2 mg and 1.0 mg per day is recommended for older (more than 51 years old) men and women respectively, even though they consume less than 2000 kcal daily, because older persons use thiamine less efficiently (Krause and Mahan, 1984; McCormick, 1986; Sauberlich et al., 1979; Suter et al., 1987). The calorie-corrected thiamine intake of the elderly is above the recommended 0.5 mg/1000 kcal.(Suter et al., 1987). It was found that older women react more rapidly to thiamine depletion and respond more slowly to partial repletion than do younger women (Oldham,1962).

3.1.4 Absorption, transport and metabolism

Absorption. Thiamine is absorbed readily in the acid medium of the proximal duodenum and to some extent in the lower duodenum (Krause and Mahan, 1984). It is absorbed by an active transport process that is probably carrier-mediated so long as intake is less than 5 mg/day; at higher intakes, massive diffusion increasingly contributes to absorption (Rindi and Ventura, 1972; McCormick, 1986; Wilson, 1987).

Thiamine in intestinal cells probably is derived from two sources: one is by the entry of thiamine from the mucosal side via a process linked either with phosphoryla-

tion or with Na^+ and the other by the dephosphorylation of thiamine phosphates into thiamine within the cell. The lack of Na^+ may inhibit the process of dephosphorylation rather than the process of thiamine entry (Rindi and Ventura, 1972).

The exit of thiamine is dependent on Na^+ and is linked with the normal function of ATPase at the serosal pole of mucosal cells (Rindi and Ventura, 1972). The absorption of thiamine is not affected significantly by food (Levy and Hewitt, 1971).

In experimental rats, approximately 46% of thiamine is eliminated in the faeces and 16% in the urine, a total of 62% being excreted. In man the capacity of the intestine to absorb thiamine, when the intake is 20-40 mg daily, ranges from 8 to 14 mg; an increase in the faecal excretion occurs when 3-5 mg is given daily. Increased faecal excretion occurs in a 100-g rat when 0.12 mg are fed. On a body weight basis this would be 1.2 mg/kg for the rat and 0.07 mg/kg in man.
It has been pointed out that the blood levels of B-vitamins are correlated with the body requirements (Da Silva and Ivy, 1961).

Transport. Thiamine is phosphorylated in the mucosal cells of the jejunum to thiamine pyrophosphate and in this form is carried to the liver by the portal circulation (Krause and Mahan, 1984; McCormick, 1986).

McLane et al. (1987) found increased axonal transport in peripheral nerves of thiamine deficient rats. The increase in transport suggests that thiamine deficiency per se has no detrimental effect on the transport machinery and process, but may indicate extensive regenerative activity in the distal portions of these axons.

Thiamine deficiency enhances the transmural flux of low concentrations of glucose (1 to 10 mM) However, the transmural flux at 15 and 20 mM glucose was unchanged. Ethanol ingestion decreases the maximal transport velocity (J max) of glucose and obviates the enhancement of glucose transport in thiamine deficiency. Ethanol inhibits glucose transport across the brush border membrane, but not across the serosal membrane and it depresses selectively the activity of sucrase, maltase, and lactase. The depression of the activity of these membrane-bound enzymes suggests that ethanol may alter the physical properties of the cell membranes (Hoyumpa et al, 1981).

The intestinal uptake of glucose, glycine, alanine and leucine was elevated in thiamine deficient rats. Studies with glucose and glycine revealed that stimulation of the absorption process occurs only in the presence of Na^+ but not in its absence.

A decrease in the thickness of the unstirred water layer at the luminal surface of enterocytes (Hoyumpa et al., 1981) together with thinning of the microvillus membranes in thiamine deficiency, presumably contributes to observed changes in kinetic parameters of glucose and glycine transport systems in the intestine, which lead to enhanced nutrient absorption (Mahmood et al., 1984).

The activities of brush border sucrase, lactase, maltase, alkaline phosphatase and leucine aminopeptidase were reduced by 42-66% in thiamine deficiency. Kinetic studies with sucrase and alkaline phosphatase evinced that a decrease in V max (maximal velocity) with no change in Km (affinity constant) was responsible for observed impairment in the enzyme activities

Thiamine deficiency may lead to accumulation of pyruvate and other metabolites, and to an impairment in the operation of the tricarboxylic-acid cycle, thus affecting the production of ATP. This in turn may influence the biosynthetic activities of the intestinal tissue and a decrease in the levels of various brush border enzymes (Mahmood et al., 1984).

Metabolism. The three tissue enzymes known to participate in the formation of the phosphate esters are:

1. Thiaminokinase (a pyrophosphorylase), which catalyzes formation of thiamine pyrophosphate (TPP) and adenosine monophosphate (AMP) from thiamine and adenosine triphosphate (ATP).
2. TPP-ATP phosphoryl-transferase, which forms the triphosphate and adenosine diphosphate (ADP) from TPP and ATP
3. Thiamine-triphosphatase, which hydrolyzes TPP to the monophosphate.

Thiaminokinase is found widespread, whereas the other two enzymes are mainly found in nervous tissue.

It is known that thiamine is converted into thiamine diphosphate in the animal body. In addition to thiamine diphosphate, thiamine triphosphate (TTP) is present in organs such as the liver, kidney and brain; the function of this metabolite, however, is not yet clear. It was reported that thiamine triphosphate, like adenosine triphosphate, is hydrolyzed to phosphate and thiamine diphosphate by myosin In addition, it was shown that thiamine triphosphate is used as a phosphate donor for the phosphorylation of glucose.

Apart from thiamine diphosphate and thiamine triphosphate, thiamine monophosphate was found in peripheral nerves. The forms present in greatest quantity were thiamine di- and monophosphate (Wiss and Brubacher, 1962).

Thiamine, as well as several of its catabolites, is excreted into the urine by the renal tubules. The principal urinary catabolites of thiamine are: 2-methyl-4-amino-5-formylaminopyrimidine; thiamine acetic acid; 2-methyl-4-amino-5-pyrimidinecarboxylic acid and 4-methylthiazole-5-acetic acid (McCormick, 1986).

The depletion of thiamine in liver, kidney and heart follow an essentially exponential curve, but the brain holds on to its thiamine without loss until a critical point is reached, after which it is rapidly lost (Holt and Snyderman, 1955).

3.1.5 Thiamine in the body

The free thiamine occurs in the plasma, but the coenzyme, TPP, predominates in the cellular components. Approximately 30 mg, 30 times the daily nutritional requirement (Truswell, 1985), is stored in the body with 80% as the pyrophosphate, 10% as triphosphate, and the rest as thiamine and its monophosphate

In normal, stock diet-fed animals, about 30% of total liver TPP is localized in the mitochondria while the rest is found almost exclusively in the supernatant fraction (including microsomes). Free thiamine is distributed between the supernatant (65%) and the nuclear fraction (23%) (Marfatia et al., 1960).

About half of the body's stores are found in the skeletal muscles, with much of the remainder in heart, liver, kidneys, and nervous tissue, including the brain, which contains most of the triphosphate. (McCormick, 1986; Truswell, 1985).

The thiamine content in the body varies greatly. In the heart muscle, 2-3 μg/g, in brain, liver and kidneys about 1 μg/g and in skeletal muscles 0.5 μg/g (Goldsmith, 1953; Victor et al., 1989).

In man, as judged by the analysis of autopsy specimens, the ceiling level of thiamine is 1.0 to 1.5 μg/g of body weight. The total in the entire body is about 70 to 100 μg, much lower than in the rat per gram of body weight (Williams, 1961).

3.1.6 Functions (McCormick, 1986; Krause and Mahan, 1984)

Thiamine is a pyrimidyl-substituted thiazole [3-(4-amino-2-methyl-pyrimidyl-5-methyl)-4 methyl-5-(ß-hydroxyethyl) thiazole].

In vegetable foods, thiamine exists mostly in the free, non phosphorylated form, and in meats as thiamine pyrophosphate (TPP). Ingested, thiamine must be converted into the phosphorylated form in order to become active as a cofactor. This conversion, which probably takes place in all cells that require thiamine, is carried out with adenosine triphosphate (ATP). In the tissues, practically all thiamine is present in the phosphorylated form.

TPP or cocarboxylase acts as a coenzyme for pyruvate dehydrogenase for the oxidative decarboxylation of pyruvate to form active acetate and then acetyl coenzyme A as a biosynthetic precursor to other essential compounds such as lipids and acetylcholine of the parasympathetic nervous system.

TPP participates as a coenzyme in alpha ketoglutarate dehydrogenase, which is required for the oxidative decarboxylation of alpha ketoglutaric acid and the 2-ketocarboxylates in the citric acid (Krebs) cycle. These ketoacids are derived from the amino acids methionine, threonine, leucine, isoleucine and valine.

TPP functions as a coenzyme for transketolase, a constituent enzyme of the hexose monophosphate shunt, an alternate pathway for glucose oxidation. This cycle provides pentose phosphate for nucleotide synthesis and reduced NADP (nicotinamide adenine dinucleotide phosphate) for various synthetic pathways such as fatty acid synthesis.

Thiamine has a specific role in neurons, independent of its coenzymatic function in general metabolism Thiamine and its esters are present in axonal membranes, and electrical stimulation of nerves effects the hydrolysis and release of thiamine diphosphate, and triphosphate (Wilson, 1987). The cyclic dephosphorylation and rephosphorylation promotes the passage of ions, probably sodium, across the membrane (Victor, 1984).

Excitation of the vagal nerve results in a "release" of thiamine into the heart (Von Muralt, 1962) and activation of the sodium transport system.

3.1.7 Antithiamines

A thiamine antagonist is a compound that can compete with thiamine or thiamine derivates in enzymatic reactions. Antithiamines may be divided into three distinct categories (Rogers, 1962):

1. Classic inhibitors
2. Thiaminase
3. Anticoccidial inhibitors.

3.1.7.1 Classic inhibitors = antivitamins = thiamine antagonists

The two most thoroughly studied inhibitors are pyrithiamine and oxythiamine. They differ markedly in their toxic manifestations; only the former produces polyneuritis in mice. Pyrithiamine and oxythiamine are pyrophosphorylated enzymatically and function as cocarboxylase antagonists in pyruvic decarboxylase and transketolase reactions (Rogers, 1962).

The action of these vitamin antagonists is that they so closely resemble the vitamin that they can enter into combination with the apoenzyme in place of the true

coenzyme. They cannot perform its function as a catalyst, but they block the true coenzyme from doing its function (Williams, 1961).

Pyrithiamine inhibits phosphorylation of the thiamine, thereby preventing the formation of metabolically active cocarboxylase.

3.1.7.2 Thiaminases

Thiaminases are enzymes that have antithiamine activity (ATA). They occur in certain fishes, fruits, vegetables, bacteria, et cetera.
There are two kinds of thiaminases (Vimokesant et al., 1975; Murata, 1982): Thiaminase I is found in shellfish, fresh-water fish (mainly in viscera), fern and a limited number of sea fish and plants, and produced in microorganisms such as Bacillus and Clostridium. Thiaminase II is produced in other types of Bacillus, Trichosporon, Candida, Oospora, and other organisms.They are usually inactive in living cells, but are activated when they are homogenized in a water solution around pH 4-8 or excreted from cells or microorganisms into the medium. Thiaminase I catalyzes the cleavage of thiamine by an exchange reaction with an organic base as well as with a sulfhydryl compound involving a nucleophilic displacement on the methylene group of the pyrimidine moiety of thiamine. On the other hand, thiaminase II simply accelerates the hydrolysis of thiamine into its pyrimidine and thiazole moieties.

Fish and other seafood. The presence of thiaminases in fish appears to be more pronounced in fresh water fish than in ocean fish. The liver of tuna and papio has three to four times the antithiamine activity registered in the muscle. Other organs such as intestine, kidney and liver generally show higher activity than seen in the muscle. Not all the antithiamine activity can be destroyed by heating, which illustrates that a thermostable thiamine-destroying factor is present.

The presence of ATA should be considered in the use of fish flour as a high-protein food supplement for human use and also in the use of fish products in animal food. (Hilker and Peter, 1966).

Raw, fermented fish, as is consumed in Thailand, has ATA (Vimokesant et al., 1975). Mussels, oysters and crabs produce ATA (Erbslöh and Abel, 1970). Clams, shrimp and carp viscera contain thiaminase (Williams, 1961). Thiaminase in fish splits thiamine into its pyrimidine and thiazole components, i.e.: 2-methyl-6-amino-5-hydroxymethylpyrimidine and 4-methyl-5-hydroxyethyl-thiazole (Williams, 1961).

Tea. Of the various teas tested by Hilker et al. (1974) the black tea and instant tea had the lowest antithiamine activity. The ATA of teas appears to be related to their tannin content. Tea contains numerous polyphenol compounds, a characteristic one being tannin, a complex mixture of high molecular weight polyhydroxy-phenols which gives tea its astringent taste. Since tannins comprise 7 to 14% of tea leaves' dry weight, tea would be expected to have antithiamine activity (ATA). Thiamine destruction by tea increases markedly and linearly after pH 7, until complete destruction is achieved at pH 7.5. The higher destruction of thiamine by tea occurs at 60 °C (Hilker et al., 1974).

Both tea drinking and chewing fermented tea leaves, which is practiced in the northern provinces of Thailand, have a significant deleterious effect on the thiamine status (Vimokesant et al., 1974).

Coffee. Coffee contains ATA. The active agents are 3,4 - dihydroxycinnamic acid, chlorogenic acid and pyrocatechine (Boenicke and Cameron, 1969; Somogyi et al., 1976).

Plants and fruits. A large number of vegetables and fruits have ATA, such as blueberries, red chicory, black currants, red beet root, Brussels sprouts, red cabbage, ferns (Leevy and Habba, 1987), betel nuts (Vimokesant et al., 1975), white cabbage (Brassica oleacea), (Linn), cassava leaves (Manihot utilissima), (Pohl), Phaseolus vulgaris (French beans, butter bean, snap bean, string beans, called "buncis" in Indonesian), Indonesian Amaranth (Amaranthus hybridus L, or "bayam"), Vigna sinensis (cowpea, yard long bean), Gnetum gnemon (a leafy vegetable called "daun melinjo") have ATA (Dawiesah, 1983).

Hilker (1968) reported that there are at least four factors regarding ATA in blueberries, one of which is 3,4 dihydroxy-cinnamic acid. Bracken fern (Pterisaguilina), which causes serious outbreaks of "fern poisoning" in cattle, is thermostable. Weswig et al. (1946) did not note any decrease in the toxicity of air-dried ferns when heated at 105 °C in air for 18 hours. The ATA of betel nuts is suspected to be related to their high tannin content (Vimokesant et al., 1975). Many compounds with orthodihydroxyphenol groups contain high ATA; such compounds are common in plant materials (Vimokesant et al., 1975).

Bacteria. Thiaminases are also produced by the thiaminolytic bacillus, aneurinolytic bacillus, and the thiaminolytic clostridium (Matsukawa, 1956; Murata, 1965). Murata (1965) estimates that 15% of the beriberi cases in Japan are caused by thiaminase, in 3% of which thiamine deficiency develops due to an infection with the thiaminolytic bacillus.

Others. Furosemide is an antidiuretic which has antithiamine activity (Yui et al., 1980).

3.1.7.3 Anticoccidial inhibitors

Amprolium blocks the absorption of thiamine in chicks and laying hens. It is possible that a similar absorption block accounts for the anticoccidial action. At higher levels of amprolium, thiamine absorption in chicks is blocked, while at lower levels, thiamine absorption by the coccidia is blocked (Roger, 1962).

3.2 THIAMINE DEFICIENCY

3.2.1 Classification of thiamine deficiency

Thiamine deficiency is classified into several types.
Krause and Mahan (1984) classify thiamine deficiency into:

- Early stage of deficiency
- Wet beriberi [classic (chronic or subacute) type and acute fulminant (shoshin or acute pernicious) type]
- Dry beriberi (beriberi polyneuropathy and Wernicke-Korsakoff syndrome (Notermans et al., 1990 ; Djoenaidi, 1991)
- Acute, mixed type of beriberi
- Infantile beriberi.

3.2.2 Epidemiology

Thiamine deficiency is not uncommon in countries where polished rice is the staple diet (Djoenaidi et al., 1990). In the West this disease was reported in association with alcoholism (Notermans et al., 1990). No acceptable incidence or prevalence study of beriberi polyneuropathy has been carried out for developing countries. A few reports have been published on Asia and Africa. The most extensive survey in recent years was conducted in China (Chen et al., 1984).

The distribution of the various forms of thiamine deficiency among 2321 peasants in a province of South China was as follows: dry form 64%, wet form 1 4% and mixed form 34.6%. 72.3% of these patients were between 15 and 44 years, children (<15 years) and older patients (>60 years) were less affected, i.e. 5.2% and 6%, respectively. Men were more affected than women in a ratio of about 2.1. The peak of occurrence was in the month of May and only rare cases were found in February and August The average intake of thiamine in these patients was 0.22 - 0 26 mg/1000 kcal. Beriberi did not occur when the intake was higher than 0.34 mg/1000 kcal
The consumption of highly polished rice, and little meat or legumes, in combination with excessive physical labour is the main cause of thiamine deficiency in these peasants. Of their total thiamine intake, approximately 30.6% came from cooked rice, 19.6% from the water in which rice was cooked, 41.3% from vegetables and 8 5% from meat (Chen et al., 1984).

A marked increase of beriberi in the army has been reported by Khmer physicians after the influx of United States polished white rice. Dry beriberi was much more common than wet beriberi (Everett, 1979).

In a study of thiamine deficiency in children in Northern Thailand, Thanangkul (1975) found a reduced excretion of thiamine in urine (24 hour) in up to 9% of children. These findings indicate that thiamine deficiency in children is less common.

Wadia (1984), in a 3-year prospective study of 67 consecutive malnourished patients admitted for neurological symptoms to a teaching hospital in Bombay, found that 28 patients (41.8%) had peripheral sensory neuropathy The peripheral neuropathy was probably caused by thiamine or multivitamin B deficiency Strict vegetarianism, food fads, alcoholism, chronic infections such as pulmonary tuberculosis, and multiple pregnancies were also factors.

Studies in South Africa suggest that beriberi occurs seasonally or is underdiagnosed. Replacement of traditional cereals by overmilled, imported staple foods is the probable causal factor. In 1988, an outbreak of beriberi occurred in The Gambia during the rainy season. At least 140 people were affected, and 22 died Attack rates were highest in young adults (20-29 years), the majority of whom were males ($\sigma^{\prime} \cdot \varphi$ = 4.5 : 1). All patients had peripheral oedema and one-third had a mixed motor and sensory neuropathy. Cardiac beriberi was less common. Gradual replacement of traditional cereals with imported milled rice may have increased susceptibility to beriberi. The inhabitants are virtually all teetotalling Muslims, whose staple diet is millet and milled rice imported from Thailand Fish, vegetables and fruit are only occasionally available. All these factors, combined with high rainfall, high agricultural workload, cooking methods, and possible thiamine antagonists, may have led to the outbreak (Tang et al., 1989)

The prevalence of thiamine deficiency in the civilian population of the settled !Kung San, living in the northern Kalahari Desert in Namibia, was 30 2% among men and 20% among women. Overall 27% of the subjects had low thiamine levels The staple food, commercial maize meal, is consumed as a porridge, or fermented with cane sugar to make beer (van der Westhuyzen et al , 1987)

In a population study, Osuntokun (1984) found a prevalence rate of symmetrical polyneuropathy of 7 per 1000. In a series of 358 patients with peripheral nerve disorders, 10.1 percent were caused by nutritional deficiency. The most commonly observed vitamin deficiency in nutritional neuropathies in Africans is thiamine deficiency. It is more often seen in males than in females. The predisposing factors are poverty, lack of care of food, diarrhea, malabsorption, excessive vomiting from pregnancy or disease states, mental illness, anorexia, compounding factors such as periodic drought or famine, and ignorance. Precipitating conditions include pregnancy, lactation, febrile illnesses and alcoholism.

Thirteen dry beriberi cases have been reported from North-West Ethiopia. All cases were of young males with a mean age of 23 5 years. It took at least 6 weeks, on the average, to recover from the disease with thiamine therapy. A carbohydrate-rich diet, little meat, excessive physical work, high atmospheric temperatures of up to 46 °C, and malaria were assumed to be the main causes (Mengistu and Maru, 1979). Demeke and Habte-Gabr (1982) suggested that thiamine deficiency in all its forms might be a more common problem in Ethiopia than is suspected. They mentioned mild symptoms of rheumatism, burning pain to frank neuro-muscular and cardiac manifestations as the clinical features suggestive of thiamine deficiency.

Thiamine deficiency may also be an additional deficiency in malnourished children as shown in Jamaica. Subclinical thiamine deficiency was found in 7% of normal children and in 36% of malnourished children in Jamaica (Hailemariam et al., 1985).

3.2.3 Stages of thiamine deficiency

Thiamine deficiency may be divided into the following stages (Brin, 1964):

Stage I: Preliminary (time of onset 5 days)
Urinary thiamine is reduced to 50 μg/day, due to dietary inadequacy, malabsorption and/or abnormal metabolism

Stage II: Biochemical (time of onset 10 days)
Red blood cell transketolase activity is depressed with a positive TPP effect of about 15%. Urinary thiamine is reduced to 25 μg/day

Stage III: Physiological (time of onset 21-28 days)
Loss of body weight concurrent with appetite loss, general malaise, insomnia, increased irritability. Urinary thiamine less than 0.25 μg/day. Red blood cell transketolase activity reduced 15-25% with a TPP effect of up to 30%.

Stage IV: Clinical (time of onset 30-300 days)
Increased malaise, loss of body weight, intermittent claudication and polyneuritis, bradycardia, peripheral edema, cardiac enlargement, ophthalmoplegia. Urine thiamine negligible; red blood cell transketolase activity reduced more than 35%; TPP effect in excess of 40% (estimated).

Stage V : Anatomical (time of onset 200 days or more)
Cardiac hypertrophy, degeneration of granular layer of cerebellum, perivascular cerebral hemorrhages with degeneration of neurones and processes, swelling of microglia and proliferation of astrocytes, mamillary body pathology. Urine thiamine negligible; red blood cell transketolase depressed in excess of 45%; TPP effect in excess of 50% (estimated).

Truswell (1985) divides thiamine deficiency into 3 stages :

Stage I: (Compensation or adaptation)

The patient adapts to the low intake ; urinary excretion of thiamine or its metabolites typically falls but there is no evidence of abnormal function or of depletion of the cells.

Stage II: (Functional)

In the second stage there are also biochemical changes indicating either impaired function or cellular depletion, but clinical manifestations of deficiency are absent or non- specific. The red blood cell transketolase activity is reduced and the TPP effect is more than 25%.

Stage III: (Clinical)

The third stage of depletion is that of the clinical deficiency disease.

3.2.4 Etiology and factors influencing thiamine deficiency

Deficiency in the diet/intake. Poverty; a high-carbohydrate diet with little or no meat, legumes or nuts, is the main cause of thiamine deficiency in the low socio-economic groups in Indonesia (Djoenaidi and Notermans, 1990).

Stomach cancer; pyloric stenosis; hyperemesis gravidarum; prolonged voluntary fasting or hunger strikes; alcoholism; parenteral nutrition for longer periods of time with hypercaloric diets or dextrose; strict slimming diet; refeeding after starvation; modern processed foods such as soybean products, evaporated milk, etc , may precipitate thiamine deficiency (Cochrane et al., 1961; Feuerlein, 1977; Sotaniemi and Kaarela, 1977; Anonymous, Lancet 1979; Devathasan and Koh, 1982; Anderson and Charles, 1985; Reuler, 1985; McCormick, 1986; Davis and Wolf, 1958).

Defective intestinal absorption. Malabsorption states, alcoholism, chronic malnutrition (Wilson, 1987) cause defective intestinal absorption of thiamine. In Western countries, folate deficiency is most commonly associated with chronic alcoholism and is often complicated by multiple deficiency of other vitamins especially of thiamine (Howard et al., 1974). In folate deficient rats, there was a significant (30-50%) decrease in duodenal and jejunal absorption of low doses of thiamine hydrochloride (0,5 μM); whereas high doses of thiamine (17.5 μM) were assimilated normally (Howard et al., 1974).

Borst (1980) diagnosed severe heart failure due to beriberi in a man, who for several months had taken large amounts of a combination preparation containing magnesium trisilicate and aluminium hydroxide for reflux oesophagitis due to a sliding hiatus hernia. It was found, that in vitro, magnesium trisilicate absorbs relatively large amounts of thiamine; consequently, chronic use of it may severely impair the intestinal absorption of thiamine.

Glad et al. (1978) and Vyas et al. (1980) reported dry beriberi following jejuno-ileal bypass surgery for morbid obesity The malabsorption resulting from an extensive intestinal bypass impairs thiamine uptake into the intestinal mucosa.

Accelerated loss. Diuretic therapy, hemodialysis, peritoneal dialysis and diarrhea cause accelerated loss of thiamine (Wilson, 1987; Anonymous, Lancet 1979, Jagadha et al., 1987).

Increased requirement (metabolism). Pregnancy, during lactation, thyrotoxicosis, fever of unknown origin, and chronic febrile infection cause increased requirement of thiamine (McCormick, 1986, Wilson, 1987; Anonymous, Lancet 1979).

Failure of utilization. Deficits of nucleogenic vitamins, zinc or protein may interfere with the conversion of thiamine into transketolase, thus producing clinical features of beriberi despite the presence of normal thiamine blood and tissue levels (Leevy and Habba, 1987).

In addition, even with normal thiamine levels and transketolase activity, symptoms of a thiamine deficiency may occur because of the absence of precursors of RNA or DNA (Leevy and Habba, 1987)

Magnesium deficiency (a cofactor of thiamine-dependent enzymes) also causes failure of thiamine utilization (Itokawa, 1987; Dyckner et al., 1985).

Some patients may have a genetic abnormality in the kinetic properties of transketolase (diminished binding capacity of the coenzyme thiamine pyrophosphate to the apoenzyme), thus predisposing them to Wernicke's encephalopathy (Blass and Gibson, 1977).

Thiaminases. Thiaminases are substances from vegetables, fruits, fishes, bacteria etc., which have antithiamine activities.

Immunology. Nutritional polyneuropathy may be due to the development of an immune state caused by accumulation of antibodies to vitamin receptors or apoenzymes. Since the latter consist of protein, they are potentially antigenic The presence of antibodies to apoenzymes would necessarily increase the daily requirements of the vitamin involved, and the patient would be more susceptible to nutritional depletion (WHO technical report series,654, 1980)

Genetic predisposition. A genetic predisposition to alcoholism has been demonstrated in the sons of men with early onset alcoholism (Cloninger, 1987). Possible biologic markers of a genetic predisposition have also been identified in human cells, including altered stimulation of cyclic AMP production in lymphocytes and platelets (Diamond et al., 1987 ; Nagy et al., 1988; Tabakoff et al., 1988), increased inhibition by ethanol of monoamine oxidase in platelets (Tabakoff et al., 1988), decreased maximal activity of monoamine oxidase in platelets (Faraj et al , 1987), reduced affinity of transketolase for thiamine pyrophosphate in fibroblasts (Mukherjee et al , 1987), and increased synthesis of phosphatidylethanol in lymphocytes (Mueller et al , 1988)

Additional putative markers of alcoholism in the male progeny of alcoholic fathers include alternations in event-related electroencephalographic potentials (Begleiter et al., 1984; Polich et al., 1988), diminished ethanol-induced stimulation of prolactin secretion (Schuckit et al., 1987) and resistance to ataxia produced by ethanol (Schuckit, 1985). Inherited abnormality of thiamine-dependent transketolase, which reduces its affinity for thiamine, is found in some individuals (Blass and Gibson, 1977).

Thiamine related inborn errors of metabolism There are several thiamine related inborn errors of metabolism: lactic acidosis due to low activity of pyruvic decarboxylase in the liver; intermittent cerebellar ataxia related to abnormal pyruvate dehydrogenase (Leevy and Habba, 1987, Wilson, 1987); thiamine-dependent megaloblastic anemia for which the mechanism is unknown (Viana and Carvalho, 1978, Mandel et al., 1984; Abboud et al., 1985, Wilson, 1987), thiamine-responsive maple syrup urine disease with branched chain ketoaciduria which is due to low

activity of a ketoacid dehydrogenase (Scriver et al., 1985; Leevy and Habba, 1987), and subacute necrotizing encephalopathy (Leigh's disease) associated with a decrease in tissue thiamine triphosphate. This deficiency appears to result from the presence of an inhibitor in body fluids which prevents the formation of TTP (thiamine triphosphate) from TPP (thiamine pyrophosphate) by inhibiting TPP-ATP phosphoryl-transferase, the enzyme which catalyzes the formation of TTP (Pincus et al, 1973, Leevy and Habba, 1987).

3.2.5 Biochemical findings

Thiamine in blood. The thiamine content of blood, determined by Sauberlich (1967), is reduced about 15-20% in patients with beriberi. The mean value is 37 ± 11 SD ng/ml in healthy control subjects, 21 ± 12 SD ng/ml in alcoholics with neuropathy without significant liver disease, and 11 ± 9 SD ng/ml in patient with neuropathy and active cirrhosis (Fennelly et al., 1967).
Whole blood and serum values of thiamine by a simplified thiochrome method in 44 healthy adults ranged from 11.3 to 47.8 mμg/ml (mean 29.3) and from trace amounts to 20.5 mμg/ml (mean 10.2), respectively (Myint and Houser, 1965).

Ideally, the blood thiamine level and red blood cell transketolase activity should be known prior to treatment. The blood thiamine level furnishes an index to thiamine stores, while red blood cell transketolase activity provides information on ability to convert thiamine into its metabolically active form (Fennelly et al , 1967)

However, blood thiamine and thiamine pyrophosphate determinations have not been particularly helpful in the diagnosis of nutritional thiamine deficiency The decreases in blood thiamine encountered in beriberi patients are not great, and considerable overlapping of values with those of normal subjects occurs (Brin, 1964) Thiamine blood levels in normal subjects vary considerably from day to day (Sauberlich, 1967). Since the depression of blood thiamine is small even in frank beriberi, their use has been found impractical (Brin, 1964).

Microbiological assay. It has been suggested that microbiological assay by the flagellate Ochromas Danica is a more sensitive method of determining the thiamine nutritional status than by the thiochrome method (Baker, 1967).

Red cell thiamine is determined by automated microbiological assay, using a chloramphenicol-resistant mutant Lactobacillus Fermenti as test organism and thiamine pyrophosphate standards. The organism responds to both thiamine hydrochloride and its esters and to free and bound forms of the vitamin. Red cell thiamine reflects tissue concentrations of the vitamin (van der Westhuyzen, 1987)

Urinary thiamine. Thiamine levels in 24-hour urine samples reflect dietary thiamine intake, ranging from 100 micrograms when intake is 0 5 mg/1000 kcal, to 5-20 micrograms at an intake of about 0.2 mg/1000 kcal (Pearson, 1962, Sauberlich, 1967) The validity of urinary thiamine as an indicator of (reduced) thiamine intake is illustrated by experimental human studies (Brin, 1963; 1964).

According to Brin (1964), in the preliminary thiamine deficiency stage (5 days after onset) urinary thiamine is reduced to 50 μg/day, in the biochemical thiamine deficiency stage (10 days after onset) thiamine excretion in the urine decreases to 25 μg/day; in the physiological stage (21-28 days after onset) is reduced to 0 25 μg/day, and in the clinical (30-300 days after onset) and anatomical (200 or more days after onset) stages, urinary thiamine is negligible

Although urinary thiamine is not an appropriate indicator for beriberi, it is useful to assess the adequacy of dietary intake in surveys of population groups (Tanphaichitr et al., 1970). One should, however, be cautious in the interpretation of results if the fluctuations in dietary intake are large (Bamji, 1970). In practice, it will be difficult to obtain 24-hour urine samples. The indicator of thiamine per unit of creatinine (mg/g) in random urine samples is used to overcome this constraint

Red blood cell transketolase. Horecker and Smyrniotis (1953) and Racker et al. (1953), independently, discovered that transketolase, one of the enzymes of the hexose-monophosphate shunt, requires thiamine pyrophosphate as a cofactor.

Transketolase has been found in yeast, spinach and in the cytoplasm of animal cells, including those of the brain. It acts as a catalyst in the following reactions (Dreyfus, 1962; Dreyfus and Victor, 1961; McIntyre and Stanley, 1971):

(1) Xylulose-5-phosphate (X-5P) + Ribose-5-phosphate (R-5P) ⇌ Sedoheptulose-7-phosphate (S-7 P) + Glyceraldehyde 3-phosphate

(2) Xylulose-5-phosphate (X-5P) + Erythrose-4-phosphate (E-4P) ⇌ Fructose-6-phosphate + Glyceraldehyde 3-phosphate

There are two methods of determining transketolase activity: the chemical method (Dreyfus, 1962; Brin 1963) and the enzymatic method (NADH-dependent transketolase assay) (Jeyasingham et al., 1987).

Method of Brin (1963). For this purpose red blood cells are removed from freshly drawn whole blood by centrifugation at 3000 rpm and washed twice with saline, the cells are hemolyzed by adding an aliquot of distilled water. The red blood cell transketolase results are expressed in micrograms of hexose utilized per milliliter of red blood cell hemolysate per hour. The red blood cell transketolase activity of less than 850 μg/ml per hour without added TPP is considered deficient (Brin, 1963). The two factors complicating application of this method in routine studies are the absolute requirement of freshly shed cells and the use of isotopes in the Warburg (Brin et al., 1960).

Micromethod of Dreyfus (1962). This micromethod of measuring blood transketolase activity by Dreyfus is simple and reproducible and is of value in nutritional surveys among infants and children, as well as in the assessment of marginal thiamine deficiency states.

In brief, this method consists of the incubation of samples of hemolyzed whole blood with an excess of D-ribose-5-phosphate substrate, both in a plain buffered medium and a medium containing an excess of TPP. The sedoheptulose-7-phosphate (S-7-P), elaborated after an incubation period of 30 minutes at 38 °C, is then measured spectrophotometrically and the results are expressed as micrograms of sedoheptulose-7-phosphate produced per milliliter of hemolysate per hour (Dreyfus, 1962).

An average normal whole blood hemolysate transketolase value is 975 ± 32.2 μg S-7-P/ml/hour (Akbarian and Dreyfus, 1968). One international unit is equivalent to the number of micromoles of sedoheptulose-7-phosphate formed per minute per liter of blood (Chong and Ho, 1970).

In rat experiments, severe symptoms and signs of deficiency become evident when the enzymatic activity drops to 10 percent of normal (Dreyfus, 1962). Depression of transketolase activity is evident at 7 to 9 days, growth ceases at 12 to 14 days, hair coat roughens at 16 to 20 days and nervous symptoms appear in individual rats after three weeks. The defect in enzyme activity is therefore evident approximately a week

before the growth rate of young rats is affected, and one to two weeks before other clinical signs become evident (Brin et al , 1960)

NADH (Na beta-nicotinamide adenine nucleotide)-dependent transketolase assay in erythrocyte hemolysates (modification of the method of Smeet et al; Jeyasingham et al, 1987). Antecubital vein blood (20 ml) is withdrawn into a heparinized container, chilled and used within 48 hours. The blood is centrifuged at 4 °C for 10 minutes at 1000 g and then supernatant, buffy coat and fat are removed as much as possible. The cells are washed three times with physiological saline. An aliquot (100 µl) of the red blood cells is suspended in 1.9 ml of 0.1 M Tris-HCl, pH 8.0 (at 18 °C) and frozen rapidly, using liquid nitrogen. An aliquot (200 µl) of this suspension is used for the assay.
The following parameters of ratios are calculated.

S T Z	=	specific transketolase activity without addition of thiamine diphosphate (TDP). Normal: 0.503 ± 0.211 units/g of hemoglobin.
P A R (ST 0.3/STZ)	=	primary activation ratio - the ratio of the activity in the presence of 0.3 mM thiamine-diphosphate (TDP), to that in the absence of added TDP. Normal: 1.076 ± 0 085
F A R (ST 3/ST 0.3)	=	further activation ratio - the ratio of the activity in the presence of 3 mM TDP to that in the presence of 0.3mM TDP. Normal: 0.932 ± 0.094
S A R (FAR/PAR)	=	selective activation ratio - the ratio of the further activation ratio to the primary activation ratio. Normal. 0.872 ± 0 107
S A D (FAR-PAR)	=	selective activation difference; obtained by subtracting the primary activation ratio from the further activation ratio Normal. -0.143 ± 0 119

SAR and SAD are alternative ways of trying to detect the presence of forms of the apotransketolase with an abnormally low affinity for the TDP

The chief drawback of the transketolase test is that very small amounts of thiamine may restore erythrocyte transketolase levels toward normal (Anonymous, Lancet 1982). It is also conceivable that the activity of enzymes is depressed by metabolic conditions other than thiamine deficiency, such as acidosis, and liver or renal disease Non-specific effects of this kind would obviously cast serious doubts on the validity of the assay (Dreyfus, 1962). Transketolase activity indicates the ability to convert thiamine into metabolically active forms. Transketolase values are of little diagnostic value in the presence of liver disease. The levels are low and never recover, presumably because transketolase apoenzyme levels are low (Osuntokun et al., 1985; Fennelly, 1967) Reduced transketolase activity can also be due to altered protein metabolism or altered nucleic acid metabolism (Leevy, 1980). Leukocyte transketolase activity may prove to be a more sensitive index of thiamine deficiency than the erythrocyte activity (Braunwald, 1988). The leukocytes seem to have the highest enzyme activity (Dreyfus, 1962).

Thiamine pyrophosphate (TPP) effect. Brin (1963) observed that a significant enhancement of transketolase activity was elicited by the addition of TPP to the deficient thiamine hemolysates. This is referred to as the TPP effect. The TPP effect is expressed as percent stimulation of the transketolase enzyme activity by added TPP (Tanphaichitr et al., 1970)

The TPP effect is very specific, and significant elevation must therefore reflect thiamine deficiency.
In the in vitro test, the normal TPP effect is a 0 to 14% increase of erythrocyte transketolase activity (Braunwald, 1988). According to Sauberlich (1967), a TPP effect of 0-15% is acceptable, and 7% ± 0.6% is the average normal TPP effect. A TPP effect ranging between 10% and 15% suggests minimal thiamine deficiency (Akbarian and Dreyfus, 1968). A 15-24% (Brin, 1964) or 16-20% (Sauberlich, 1967) increase of TPP effect is a marginally thiamine-deficient response. Generally, a value greater than 16% can indicate a deficient state (Tanphaichitr et al., 1970).
Greater than 20% stimulation (Sauberlich, 1967) or more than 25% increase (Brin, 1964) is evidence of a clinically severe thiamine deficiency.

3.3 POLYNEUROPATHY

3.3.1 Definition

The peripheral nervous system includes the cranial nerves, the spinal nerves with their roots and rami, the peripheral nerves and the peripheral components of the autonomic nervous system (Gardner and Bunge, 1984).

Polyneuropathy (symmetrical polyneuropathy) is a generalized process producing widespread and bilaterally symmetrical effects on the peripheral nervous system. It may be motor, sensory, sensorimotor, or autonomic in its effects, and proximal, distal or generalized in its distribution (Schaumburg et al., 1983).

According to the WHO, technical report series 654, 1980: peripheral neuropathies are defined as persistent (i.e lasting longer than a few hours) disorders of the spinal and brainstem lower motor neurons and/or the primary sensory motor and/or the peripheral autonomic neurons with associated, clinical, and/or electrographic and/or morphological evidence that indicates involvement of their (peripheral) axons and/or their supportive structures.

This disease process shows clinical, electrophysiological and morphological features with varying degrees of stages, and, in addition, subclinical forms may occur. It must be realized that functionally all neurons with their axons and the peripheral nerve endings could be affected (Schaumburg et al., 1983; Notermans 1984).

3.3.2 Classification

Polyneuropathy as a clinical picture can be classified in several ways, based on clinical, morphological, neurophysiological, and etiological criteria.
In pathophysiological terms two basic forms of polyneuropathy may be distinguished (Bradley, 1974, Liveson and Spielholz, 1979, Notermans, 1984; Mendell et al , 1984).

a. Axonal neuropathy
b. Demyelinating neuropathy
c. Apart from these two basic neuropathies, a mixed form of both may occur.

Axonal Neuropathies (distal (dying back) axonopathies). Axonal neuropathies primarily affect the axon with secondary effect on the myelin sheath. Pathologically, the largest axons are usually affected. Another type of axonal disease has an ischemic pathogenesis and occurs secondary to vasculopathies The site of axonal damage is entirely related to the area of vascular pathology, which may occur anywhere along the nerve.

Demyelinating neuropathies. The site of attack is the Schwann cell of the myelin sheath resulting in demyelination of the nerve in a segmental distribution (segmental demyelination), i.e. between the nodes of Ranvier.

Mixed form. Most neuropathies are of the mixed form, with predominance of either the myelin dysfunction or the axonal involvement. We can divide the mixed form into the following types:

Primary axonal degeneration with secondary segmental demyelination, e.g uremic polyneuropathy.

Primary myelin degeneration followed by axonal degeneration, e.g. polyneuropathy due to diphteria.

In reality, however, it is very difficult to make a distinction between the primary and the secondary process.

The World Health Organization Technical Report Series 653, page 38 (1980) classifies peripheral neuropathies also into: axonopathies, myelinopathies, and other types.

Several parameters may be used as the basis for classification:

1. By predominance of the cardinal features· Motor, sensory, autonomic or mixed nerve involvement (motor ± sensory ± autonomic).
2. By distribution of involvement: Distal, symmetrical limb, mononeuropathy, mononeuropathy multiplex, localized neuropathy (i.e. brachial), radiculopathy.
3. By time course: Acute (abrupt onset, fast evolution), subacute, chronic (slow onset and evolution), relapsing (acute or chronic with partial or full recovery in the interval)
4. By predominant pathological features:
   Axonopathy: morphological abnormality is present in axons.
   Myelinopathy: loss of myelin (often segmental, with paranodal localization) with myelinophagia by macrophages is the predominant feature.
5. By etiology or disease association.

An etiological classification conforms to the publication of Schaumburg et al (1983), who divide peripheral neuropathies into two main groups :

a. **Symmetrical Generalized Neuropathies (Polyneuropathies)**

Distal Axonopathies

Toxic -	many drugs, industrial and environmental chemicals
Metabolic -	uremia, diabetes, porphyria, endocrine
Deficiency -	thiamine, pyridoxine, etc.
Genetic -	HMSN II

Malignancy associated - oat cell carcinoma, multiple myeloma

Myelinopathies

Toxic -	diphteria, buckthorn
Immunologic -	acute Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy
Genetic -	Refsum disease, metachromatic leukodystrophy

Neuropathies somatic motor
Undetermined - amyotrophic lateral sclerosis
Genetic - hereditary motor neuropathies

Neuropathies somatic sensory
Infectious - herpes zoster neuronitis
Malignancy associated - sensory neuronopathy syndrome
Toxic - pyridoxine sensory neuronopathies
Undetermined - subacute sensory neuronopathy syndrome

Neuropathies autonomic
Genetic - hereditary dysautonomia (HSN IV)

b. **Focal (mononeuropathy) and multifocal (multiple mononeuropathy) neuropathies**
Ischemia - polyarteritis, diabetes, rheumatoid arthritis
Infiltration - leukemia, lymphoma, granuloma, Schwannoma, amyloid
Physical injuries - severance, focal crush, compression, stretch and traction, entrapment
Immunologic - brachial and lumbar plexopathy

3.4 BERIBERI POLYNEUROPATHY

3.4.1 Classification

There are several parameters as the basis for classification:
By predominance of cardinal features (Cruickshank, 1952)
- Motor: roughly 20 percent presented a purely motor symmetrical type of paresis
- Sensory: the mainly sensory symmetrical type of manifestation was established in 30 percent of the cases.
- Mixed (motor sensory): 50 percent presented the full picture of symmetrical sensory and motor paresis.

By time course (Erbslöh and Abel, 1970)
- Latent form (abortive = subclinical)
The neurological, symmetrical motor and sensory symptoms acrodistal to the legs are of a very mild nature. This form can be detected by electroneuromyography
- Acute paraplegic form
This form is very rare Anorexia and vomiting supervene within a day or two. The paralysis ascends progressively from the legs to the arms and shoulders Death from acute cardiac insuffiency often ensues within two days.
- Chronic form (slow onset and evolution).

3.4.2 Clinical features
The clinical features described here are mainly based on studies carried out by Sebrell (1962), Erbslöh and Abel (1970), Freemon (1975), Victor (1984) and Krause and Mahan (1984). They can be arranged as follows.

Early symptoms and signs. Early symptoms of adult beriberi include sensations of numbness in the feet, heaviness of the legs, and paresthesias (e.g. sensations of pins

and needles, numbness, formication and itching). Pain and tenderness in the calf muscles are common

In the early stages, the tendon reflexes may be exaggerated, whereas later they have decreased or disappeared.

Muscular weakness develops gradually, beginning in the dorsiflexors of the foot and extending to the calf muscles, the extensor muscles of the legs, the gluteal muscles and the flexors of the leg. The patient has difficulty in rising from the squatting position due to weakness of the quadriceps muscles (squat test).

Cranial nerves. The cranial nerves chiefly affected in severe beriberi polyneuropathy are the vagal, i.e. cardiac, laryngeal and recurrent nerves, causing hoarseness, laryngoparesis (aphonia), dysphagia and, especially, exceptionally prolonged tachycardia. Bilateral facial paresis has also been reported in association with severe beriberi. The nervi abducentes are sometimes affected. Other ocular nerves can be affected in association with Wernicke's encepalopathy. Deafness, numbness around the lips, weakness of the tongue have all been noted in rare instances. Subacute loss of vision, characterized by central and centrocecal scotomas and attributable to retrobulbar neuropathy, has been reported by Japanese authors in a very small percentage of cases.

Motor system. Stiffness and cramps in the muscles are the early motor signs as is an increasing muscular weakness which is most readily demonstrated by the inability of the individual to rise from a squatting position without assistance. Foot drop and wrist drop are observed in advanced beriberi. Paralysis is associated with marked muscular atrophy. The far advanced neurological changes result in great difficulty in walking and even in complete paralysis.

Sensory system. Sensory disturbances occur first on the inner surface of the legs below the knee and on the dorsum of the feet. Frequently there is a glove-stocking sensation disturbance. There is often delayed response to pain. The vibratory sense and deep sensibility are often disturbed, more severely distally than proximally. More advanced symptoms are loss of vibratory sense over the great toe and the ankle and disturbances in peripheral sensation such as paresthesias and hyperesthesia. The calf muscles are painful.

Autonomic system. The extremities are pale and cold, sometimes with profuse sweating Disturbances of sweating in the distal segments of the limbs are a common manifestation of alcoholic neuropathy. Usually sweating has decreased in these parts, but in some patients there is excessive perspiration of the feet and the volar surfaces of the hands and fingers. Probably these abnormalities are due to involvement of the peripheral (postganglionic) sympathetic efferent nerve fibres. Although postural hypotension is common in Wernicke's disease, it is observed only rarely in uncomplicated alcoholic polyneuropathy. This is probably due to the sparing of the splanchnic nerves, which are involved only in the most advanced cases of alcoholic polyneuropathy. Sometimes a dry and glossy skin is seen.

Tonus. The tonus of the muscles is flaccid or normal.

Reflexes. The deep tendon reflexes are decreased or absent, the lower extremities being more affected than the upper extremities. The abdominal reflexes and

cremaster reflexes are never suppressed, except in a very small number of cases. Pathological reflexes are not found.

3.4.3 Cerebrospinal fluid

The cerebrospinal fluid is usually normal, although a modest increase in the protein content is found in a small proportion of cases (Victor, 1984).

3.4.4 Neurophysiologic features

Motor system. Mild to moderate degrees (10-20%) of slowing of motor conduction are observed. This is caused by selective loss of the large, fast conducting fibres (Kimura, 1984). Furthermore, the conduction velocity in distal segments may be reduced, while conduction in more proximal segments is normal (Victor, 1984) In addition, the evoked muscle potential on distal stimulation is often of lower amplitude than normal (Notermans, 1984). Increase in the stimulus threshold on direct stimulation of the nerve, is more notable distally than proximally. It should be emphasized that the conduction velocity or conduction time may be normal and that the amplitude of motor potentials may be considerably reduced (Notermans, 1984). Blackstock et al (1972) found that the large motor fibres conducted normally, whereas slowing of velocity was observed in the small fibres in both alcoholic patients without neuropathy and those with clinical manifestations of peripheral nerve disease.

Sensory system. Slowing of sensory conduction and a marked reduction of the sensory action potentials are found in axonal polyneuropathy In mild cases, a reduction in amplitude of sensory potentials is difficult to establish without knowing the previous normal values (Notermans, 1984). The determination of the refractory period in the peripheral nerves, especially in the sensory fibres of the sural and median nerves, can in some cases give important and early information about the presence of a mild or even latent polyneuropathy (Notermans, 1984) Sural sensory conduction is more affected than median sensory conduction. This confirms the belief that the changes in polyneuropathy are usually more prominent in lower limb nerves (Burke et al., 1974). Lefebvre et al. (1979) found that 84 percent of their patients showed abnormalities of the sural conduction, but only 73 percent showed an abnormality of median and ulnar nerve sensory conduction in alcoholic neuropathy Sensory nerve conduction may be more affected than motor conduction, and the degree of slowing in conduction velocity is related to the severity of the polyneuropathy (Kimura, 1983)

H-reflex. Prolonged latency or reduced amplitude of the H-reflex is often one of the earliest signs of polyneuropathy (Notermans, 1984, Kimura, 1984) Lefebvre et al (1979) found 63 percent of these late response latencies to be abnormal in the evaluation of alcoholic subjects. Willer and Dehen (1977) also considered measuring H-reflex latencies to be a sensitive test for early detection of alcoholic neuropathy

F-wave. In many neuropathies of the metabolic-nutritional type, abnormalities of the F-response can be demonstrated in the same nerve where conventional methods of registering motor and sensory conduction do not show any abnormality The F-response provides additional information regarding the functioning of the alpha motor axons (Shahani, 1980). F-wave measurements are also useful in electrophysiologic studies of polyneuropathic patients and may be more sensitive than conventional motor nerve conduction velocity examinations (Eisen, 1977, Panayiotopoulos, 1977)

Data concerning the F-wave are perhaps most useful in patients with polyneuropathies, particularly those associated with prominent proximal pathology (Kimura, 1984).

Muscles. The contraction pattern is often significantly reduced and shows a diminished density: it may even be limited to discrete motor unit activity. Denervation activity is found, especially in the distal small muscles of the hand and foot, consisting of fibrillation potentials and positive spikes with increased insertion activity due to degeneration of motor axons (Notermans, 1984). Reinnervation leads to disappearance of denervation potentials. The contraction pattern will become denser and the amplitude and duration of motor unit potentials will increase, in addition to which polyphasic motor unit potentials will appear. The size of the evoked muscle response remains rather small, in contrast to the findings in primary anterior horn lesions. With single fibre electromyography it is possible to determine the fibre density of the motor unit; it is a sensitive test to establish the presence of reinnervation by the process of collateral sprouting (Notermans, 1984).

3.4.5 Pathophysiologic considerations

The major abnormality in beriberi polyneuropathy is primarily an axonal degeneration, affecting the distal segments of the peripheral nerves (dying-back neuropathy), while changes in the myelin occur secondarily (Victor, 1984). The pathological changes found in the peripheral nerves of patients suffering from beriberi polyneuropathy are identical to those found in cases of alcoholic polyneuropathy (Kimura, 1984; Notermans, 1984; Victor, 1984).

The first clinical symptoms appear distally in the lower extremities. This suggests that the first manifestation of disturbed function occurs in the extremities of the large and longest peripheral nerves (Freemon, 1975; Notermans, 1984). This may be explained by the fact that certain metabolic disorders in the cell body cause a disturbance in the supply of nutrients to the axon (axonal flow), the effects of which are apparent in the most distal parts of the axon (Notermans, 1984).

Dorsal root ganglion cells may be lost to a variable extent and the anterior horn cells of the spinal cord show an "axonal reaction". The latter alteration is probably secondary to the axonal damage in the anterior roots and peripheral nerves. Similarly, the systematic degeneration of the posterior columns, particularly of the columns of Goll, is secondary to the degeneration of dorsal root ganglion cells and posterior roots.

Appenzeller and Richardson (1966) have described unusually large neurons, in various stages of degeneration, in the sympathetic ganglia of patients with alcoholic neuropathy The lesions in the sympathetic nerves and ganglia are probably responsible for the hypotension and hypothermia in such patients, and the vagal lesions for the dysphonia and dysphagia.

3.4.6 Neuromorphological abnormalities

Light microscopy. Sural nerve biopsies of patients suffering from beriberi neuropathy viewed in light microscopy showed a depletion of the large myelinated fibres with a unimodal distribution or shift of the normal bimodality to the left. It is interesting that the myelinated fibre count varied from very low to normal, while it also varied between different funniculi of the same nerve. Degenerating and regenerating fibres were encountered, suggesting an active neuropathy (Wadia, 1984). The amount of collagen fibres had increased, and scattered fragmented myelin and myelin ovoid

formation were seen. The severity of the changes corresponded to the degree of sensory loss in the leg (Takahashi and Nakamura, 1976). The large myelinated fibres had decreased with preservation of the density of small myelinated and unmyelinated fibres. The preferential decrease of large myelinated fibres was not associated with pain in the lower limbs, a fact which is contrary to the expectation of the proponents of the gate control theory (Ohnishi et al., 1980). Myelin ovoids were frequently seen. Fibres with an abnormally thin myelin sheath relative to the diameter and demyelinated axons were occasionally found (Ohnishi et al., 1980).

Teased fibre. Teased fibre preparations showed axon degeneration in various stages in the vast majority of cases. Only a few showed concurrent segmental demyelination even of the same fibre (Wadia, 1984). Linear rows of myelin ovoids were abundant in all cases. In some patients, the relationship between internodal length and fibre diameter indicated myelinated fibres with disproportionately short internodes, suggesting axonal degeneration and regeneration (Takahashi and Nakamura, 1976).

Electron microscopy (Takahashi and Nakamura, 1976, Ohnishi et al., 1980; Wadia, 1984).

Axonal changes

Vesicles. Many flattened vesicular profiles of various sizes were observed. Sometimes there were numerous smooth vesicles of varying size, some with electron-dense cores, often in clusters, mingled with neurotubules to form islands separated by bands of neurofilaments. There were also cored vesicles and those with double membranes, probably derived from vacuolated mitochondria.

Neurotubules. The neurotubules accumulated irregularly in the axoplasm and resembled clumped neurotubules. Sometimes the tubular structures had the same orientation as the neurofilaments. Increases in and clumping of tubular structures were also found.

Neurofilaments. In addition, there were non-specific manifestations of axonal degeneration in all cases, including disorderly arrangement or rarefaction of neurofilaments.

Mitochondria. Some degenerated mitochondria were seen (vacuolated mitochondria).

Sacs. Some of the sacs showed networks encircling the neurotubules with increased density (signs of early change of beriberi neuropathy). Accumulations of sacs of various sizes were seen. They showed branching and networks. Some of the sacs may have been produced by dilatation of neurotubules, but others came from increased endoplasmic reticulum. There were myelinated fibres in which the axons were replaced by homogenous dense material. Some myelinated fibres contained floccular and electron-dense materials or glycogen granules.

Schwann cell changes

In general, changes of the Schwann cells were less than those of the axons and appeared secondary to axonal degeneration. Large myelin ovoids devoid of axons were often found in Schwann cells, as well as macrophages containing membrane-limited structure and lamellar bodies. There were a number of clusters of Schwann

cell processes (Bungner bands) in all biopsy specimens and also clusters of Schwann cells or axons, one or more of which were myelinated. The findings indicated regeneration from axonal or Wallerian degeneration.

Myelin sheath

The lamellar structure of myelin was often preserved even in fibres with degenerated axons, indicating that axonal degeneration was the primary change Changes in the myelin were less than those in the axons, and appeared secondary to axonal degeneration.

Unmyelinated fibres

Active degeneration of unmyelinated axons was occasionally found. Increased numbers of vesicular or tubular profiles, mitochondria and dense bodies were noticed in both axoplasm and Schwann cell cytoplasm in untreated patients. Non-specific degeneration of the axis cylinder, fragmentation, and rarefaction of neurofilaments were seen occasionally in all patients, but these changes were slight compared to those of the large myelinated fibres. In general it can be said, that the predominant changes were the presence of myelin ovoids in the cytoplasm of Schwann cells and granular disintegration of axoplasm. On the other hand, demyelinated axons were occasionally found. The unmyelinated fibre densities in beriberi patients and controls were similar. The density of denervated Schwann cell clusters was significantly higher in beriberi patients and the densities of nuclei of Schwann cells, fibroblasts and macrophages were similar in beriberi patients and controls.

3.4.7 Experimentally induced beriberi polyneuropathy

Since the classic experiments performed by Eijkman (1890, 1896, 1897, 1927) on chickens, numerous animal experiments have been carried out in an attempt to account for the connection between thiamine deficiency and polyneuropathy The repeated failures to produce peripheral degeneration experimentally led several authors to doubt whether thiamine was indeed the causative factor

Nevertheless, since then it has been shown by North and Sinclair (1956) that prolonged thiamine deficiency in rats produces degeneration of the peripheral nerves in excess of that caused by inanition alone Shaw and Phillips (1945) provided further evidence that chronic thiamine deficiency results in degeneration of the peripheral nerves in pigeons and they observed similar changes in chicks More recently, Prineas (1970) described the fine structural changes in the peripheral nervous system in thiamine deficient rats.

Restricting thiamine intake to 0.45 mg/day in man for up to 6 months caused anorexia and a marked but fluctuating and eventually progressive impairment of mental and physical health that took 3 months to respond fully to oral thiamine replacement (Williams et al., 1943). Eight young men consuming a 2800 kcal/day diet consisting of 80 g protein, 100 g fat and 400 g carbohydrates, and containing 0 11 to 0.18 mg thiamine, developed clinical symptoms of thiamine deficiency in 9 to 27 days (Ziporin et al., 1965).

3.4.8 Differential diagnosis of nutritional polyneuropathies other than thiamine deficiency

Alcoholic polyneuropathy. The peripheral neuropathy associated with chronic alcoholism probably results from deficiency of many vitamins including thiamine, pyridoxine,

riboflavin and folic acid (Freemon, 1975). Victor and Adams (1961) showed thiamine to be the major deficiency involved in alcoholic polyneuropathy. The study of Strauss (1935) minimizes the toxic effect upon the peripheral nerves as a significant factor in the pathogenesis of alcoholic polyneuropathy. Finally, there are no convincing data in experimental animals, that degeneration of peripheral nerves can be produced by alcohol alone (Victor, 1984). The lesions in alcoholic neuropathy and beriberi are much the same, both in distribution and in the nature of the histopathological changes (Victor, 1984; Notermans, 1984).

On the other hand, Denny-Brown (1958) drew attention to the differences between the clinical findings in beriberi and in alcoholic neuropathy: the former is characterized by symmetrical foot and wrist drop, associated with muscle tenderness, and only a mild disturbance of general sensation over characteristic areas; the latter he described as a chronic sensory neuropathy with a marked disturbance of the pain sensation and often prominent burning paresthesias in the feet, the implication being that this type is due to the toxic effects of alcohol and not to nutritional deficiency.

Alcoholic polyneuropathy is frequently associated with other signs of nutritional deprivation. The commonly observed dermal changes are generalized dryness and scaliness, pigmentation of the face (particularly over the forehead and malar eminences), acne vulgaris, thickening and overgrowth of the nose (rhinophyma), thinness and glossiness of the skin of atrophic limbs; at times frank lesions of pellagra are observed. Anemia is frequently found, usually on the basis of folic acid deficiency. Signs of liver disease were found in more than half of the cases (Victor, 1984).

Major dystrophic changes, in the form of perforating plantar ulcers and painless destruction of the bones and joints of the feet, have been observed only in rare cases (Victor, 1984).

Pyridoxine deficiency. In addition to glossitis, cheilosis, stomatitis, conjunctivitis and seborrheic dermatitis, pyridoxine deficiency produces symmetrical polyneuropathy, burning feet syndrome, optic atrophy and convulsions (Freemon, 1975). Pyridoxine deficiency is characterized by four kinds of symptoms (Erbslöh and Abel, 1970), i.e. cutaneous and mucosal symptoms, cerebral symptoms, peripheral nerve symptoms and hematological symptoms.

Pantothenic acid deficiency. Irritability, petulance and somnolence are seen in cases of pantothenic acid deficiency, followed by peripheral polyneuropathy with painful paresthesias (Freemon, 1975). Pantothenic acid is widely distributed in foods, so that a deficiency disease due to lack of the vitamin is seldom observed in man. The symptoms of pantothenic acid deficiency include: neuropsychiatric, gastrointestinal, cardiovascular symptoms and loss of antibody production (Erbslöh and Abel, 1970).

Riboflavin deficiency. Riboflavin deficiency symptoms include seborrheic dermatitis, cheilosis, pharyngeal edema, glossitis, normocytic, normochromic anemia, burning dysesthesias and hyperesthesias (Freemon, 1975).

Vitamin B12 deficiency. Vitamin B12 deficiency causes symmetrical polyneuropathy, subacute combined degeneration of the spinal cord, mental changes and megaloblastic anemia (Freemon, 1975).

Folic acid deficiency. Folate dietary deficiency has been implicated as a cause of peripheral polyneuropathy, mental changes and megalo-blastic anemia It is possible

that the polyneuropathy associated with a prolonged high dosage of diphenylhydantoin may involve folate deficiency (Freemon, 1975).

Niacin or nicotinic acid deficiency Niacin deficiency causes the triad of dermatitis (pellagra), diarrhea and dementia and probably no peripheral polyneuropathy (Freemon, 1975). Pellagra is due to a deficiency of the vitamin niacin and its precursor, the aminoacid tryptophan. Pellagra may be divided into three stages (Erbslöh and Abel, 1970):
1. The first stage is conspicuous for symptoms of nervous irritation, erythema and gastrointestinal disorders.
2. The second stage is characterized by severe cerebral and spinal defects.
3. General somatic marasmus with cachexia and usually macrocytic anemia, as well as fixed neurological and progressive cerebral lapses extending to coma are the salient features of the third stage.

3.4.9 Diagnosis

The diagnosis of beriberi polyneuropathy is based on:
- History of nutritional deficiency of thiamine.
- Clinical and neurophysiologic signs of sensorimotor neuropathy.
- Exclusion of other polyneuropathies, e g diabetes mellitus, uremia, leprosy, Guillain-Barré syndrome, hereditary and toxic neuropathy.
- Biochemical studies; for instance, erythrocyte transketolase activity (ETKA), thiamine pyrophosphate effect (TPP), red cell thiamine or the NADH (Na beta-nicotinamide adenine nucleotide)-dependent transketolase assay in erythrocyte hemolysate.
- Morphological studies. Nerve biopsies contribute to knowledge of the neuropathic process but often yield no etiological clues.
- Diagnosis pro ex juvantibus: in the absence of supportive laboratory data, the diagnosis of beriberi polyneuropathy is made on the basis of dietary history, clinical picture of sensorimotor neuropathy and the response to thiamine in follow-up studies for at least 6 weeks to 3 months (Mengistu and Maru, 1979; Williams et al., 1943).

3.5 WET BERIBERI

Wet beriberi is usually referred to as beriberi heart disease. It is also encountered in the acute, mixed type of beriberi (Krause and Mahan, 1984).
Congestive heart failure, mainly right sided, has been reported in habitual alcoholic patients living mainly on a carbohydrate and thiamine-deficient diet (Pereira et al., 1984).

3.5.1 Definition

Beriberi heart disease is characterized by evidence of biventricular failure, sinus rhythm and marked edema There is arteriolar vasodilatation and the cutaneous vessels may be dilated or, in later stages with congestive heart failure, they may be constricted A third heart sound and an apical systolic murmur are heard almost invariably and there is a wide pulse pressure characteristic of the hyperkinetic state (Braunwald, 1988).

Blankenhorn (1945, 1955) defined beriberi heart disease as follows:

1. Enlarged heart with normal rhythm (sino-auricular)
2. Dependent edema
3. Elevated venous pressure
4. Peripheral neuritis or pellagra
5. Non-specific changes in the electrocardiogram
6. No other cause evident
7. Gross deficiency of diet for three months or more
8. Improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi
9. Nutritional type cirrhosis of the liver.

Blacket and Palmer (1960) speak of beriberi heart disease if the following criteria are met:

1. An adequate history of dietary deficiency
2. Complete recovery with thiamine
3. Coexistent neuritic beriberi
4. Characteristic clinical features.

3.5.2 Classification

Cardiac beriberi (cardiovascular beriberi) presents with different clinical manifestations. It is arbitrarily divided into the classical (chronic or subacute) type and acute fulminant beriberi heart disease with lactic acidosis (acute pernicious type).

3.5.3 Classic (chronic or subacute) beriberi heart disease

The classic features are a high cardiac output with raised jugular pressure and gross edema (McIntyre and Stanley, 1971). Among the non-alcoholics especially in the East, these patients have a diet low in thiamine and high in polished rice. In the West it is often combined with chronic alcohol abuse.

The patients complain of shortness of breath especially on exertion, swelling (edema) of the ankles and lower legs (Stam and Westerhoff, 1986), numbness and a tingling sensation in the lower extremities, palpitation after walking, muscle cramps during the night. They demonstrated evidence of either peripheral neuropathy or pellagra (Blankenhorn, 1945 and 1955).

Patients with advanced beriberi heart disease display the usual signs and symptoms of biventricular failure. These include elevation of the systemic venous pressure and pulmonary wedge pressure, edema, hepatic engorgement, ascites, pleural effusion, engorgement of the veins, and rales on the bases of the lungs (Hurst 1986; Stam and Westerhoff, 1986). Characteristically, there are widening of the arterial pulse pressure and bounding peripheral arterial pulses. Pistol-shot sounds may be heard over the peripheral arteries. The heart is usually enlarged and apical diastolic gallop rhythm is characteristic (Hurst, 1986, Stam and Westerhoff, 1986, De Neeling, 1969). Hyperkinetic circulation and pulsus celer are caused by lowered diastolic blood pressure (Aalsmeer and Wenckebach, 1928).

Electrocardiogram. The electrocardiogram in patients with beriberi heart disease is usually normal except for sinus tachycardia and perhaps minor non-specific ST segment and T-wave changes (Hurst, 1986; Blankenhorn, 1945 and 1955; Akbarian and Dreyfus, 1968).

The electrocardiograms are essentially the same as those of the group with cardiac insufficiency. The rhythm is always regular (sino-auricular). Some cases show a right, others a left ventricular preponderance The voltage is low, the P-R interval is lengthened, the T-wave is negative in leads 1, 2 and 3, while it is also high in lead 2 in some of the patients (Keefer, 1930). In spite of the absence of symptoms of cardiac insufficiency, minor electrocardiographic changes are present, indicating that the myocardium is involved before symptoms of insufficiency appear.

Hemodynamic studies Hemodynamic studies in patients with heart failure due to beriberi have shown elevation of the right atrial, right ventricular and pulmonary wedge pressures, an increase in cardiac index, a decrease in arteriovenous oxygen difference, as well as a decreased peripheral resistance. All of these are typical of the high output cardiac failure (Jeffrey and Abelmann, 1971; McIntyre and Stanley, 1971; Pereira et al., 1984; Hurst, 1986).

The mechanisms of increased cardiac output in beriberi are obscure. Some patients with beriberi have lesions of the sympathetic nuclei that may decrease peripheral arterial resistance, thus increasing cardiac work and leading to congestive failure.

Pathogenesis. Most cases of cardiac beriberi are precipitated by strenuous exertion with a resultant sudden increase in thiamine requirement (Braunwald, 1988, Wolf and Levin, 1960). Increased vasodilatation and venous pooling during hot weather and any cause of fever, such as pneumonia, may induce acute cardiac failure (Wolf and Levin, 1960).

Differential diagnosis. The raised cardiac output, which is the most characteristic feature of beriberi heart disease, is not specific. It is also found in other "hyperkinetic circulatory states" such as fever, exercise, thyrotoxicosis, cor pulmonale, severe anemia, pregnancy, arterio-venous fistula, Paget's disease of bone, and advanced hepatic failure. These conditions can usually be differentiated from beriberi heart disease on clinical grounds alone (Lessard et al., 1959).
In beriberi is the therapeutic effect on thiamine distribution a good diagnostic indication. Results of ex juvantibus treatment with thiamine administration is a good evidence.

Alcoholic heart disease. In 1964 Bridgen and Robinson reviewed the main features of alcoholic heart disease, illustrating the three ways in which it may present. Firstly, with beriberi heart disease, secondly, with arrythmias, particularly atrial fibrillation and thirdly, with congestive heart failure due to large, poorly contracting ventricles with normal main coronary arteries (this is a congestive type of cardiomyopathy).

In classic cardiac beriberi in the East, right heart failure is more common than left. In alcoholic cardiac beriberi as seen in the West, however, the pattern of left heart failure with dyspnea, rales and impaired left ventricular function is more common, so that the typical mode of presentation is biventricular failure with sinus rhythm (Carson, 1982).

Physical examination of the alcoholic cardiomyopathy shows a weak pulse with small arterial pulse pressure; the cardiac output is not high. The patient frequently has atrial fibrillation and electrocardiographic signs of left ventricle hypertrophy or a bundle branch block.

In beriberi heart disease, the echocardiogram shows normal movements of the left ventricle wall, while in alcoholic cardiomyopathy the left ventricle is enlarged and

shows poor movements of the heart walls (Stam and Westerhoff, 1986). Alcoholic cardiomyopathy is of uncertain cause but is probably due to a specific chronic effect of alcohol on the heart rather than to any dietary deficiency. Atrial fibrillation is common and the characteristic feature is left ventricular failure (Carson, 1982).

Ethanol can cause cardiac muscle damage in experimental animals and is said to interfere with the activity of many enzymes within the muscle cell, directly inhibiting protein synthesis by isolated mitochondria. It also inhibits the binding of actin and myosin, probably by interfering with the binding of calcium to troponin (Anonymous, Lancet 1980). However, acetaldehyde, the first metabolite of ethanol, is a more potent depressant of myocardial function and is probably the major chemical responsible for the heart damage (Anonymous, Lancet 1980).

3.5.4 Acute fulminant beriberi heart disease (shoshin beriberi, acute pernicious type)

The shoshin form of beriberi comprises less than 5% of the cases of beriberi with cardiac involvement seen in the Orient (Wolf and Levin, 1960). "Sho" means acute damage and "shin" is heart.

According to Majoor and Hillen (1982) this fulminant form of beriberi heart disease is in the Western world not rare but easily missed The incidence rate of this disease is underestimated.

The main characteristics of shoshin beriberi are cardiomegaly with heart failure, especially the right heart, signs of cardiogenic shock, impressive peripheral cyanosis, frequently anuria, mild edema and metabolic (lactic) acidosis (Majoor and Hillen, 1982)

The acute fulminant cardiac failure is usually superimposed on a chronic beriberi state The history of alcoholism and biventricular failure, cyanosis, hypotension, high cardiac output and vasodilatation, abnormal red cell transketolase and response to thiamine with clinical recovery in the absence of other etiology of cardiac disease establish the diagnosis of shoshin beriberi (Jeffrey and Abelmann, 1971).

The clinical features and signs are as follows: fast heart rate, low blood pressure, high arterial pulse pressure, dyspneic without rales, high cardiac output despite peripheral cyanosis and cold extremities, little edema, rapid respiration but clear lungs, distended jugular veins, severe abdominal pain, extremely tender and swollen liver, and severe acidosis (Majoor, 1978; Anonymous, Lancet 1978; Majoor and Hillen, 1982).

Four phases have been described during recovery from shoshin beriberi (Naidoo, 1987):

stage 1 - phase of shock and acidosis
stage 2 - high output failure
stages 3 & 4 - diuresis and hypertension

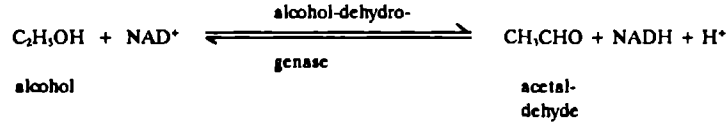
The mechanism of vasodilatation and consequent high cardiac output is not entirely understood, but accumulation of pyruvic acid and lactic acids probably plays a part. Damage to sympathetic nerves may also contribute to the vasodilatation (Anonymous, Lancet 1978; Stam and Westerhoff, 1982).

Pathogenesis of lactic acidosis in alcoholics with thiamine-deficient diet (van der Meulen, 1976; Majoor and Hillen 1982; Krause and Mahan, 1984).

Ethyl-alcohol (ethanol) is produced when yeast ferments carbohydrate. Every gram of alcohol yields approximately 7.0 kcal when completely metabolized. It is rapidly absorbed from the stomach and small intestine, uniformly distributed throughout the body water and rapidly oxidized with little or none stored. Small amounts are lost into the urine and into the respired air by diffusion.

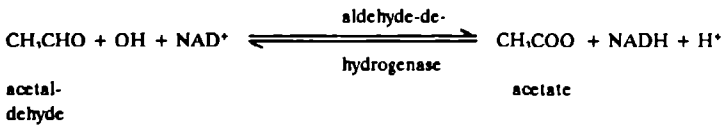
In the liver, ethanol is 90% oxidized to acetaldehyde with the aid of the cytoplasmic enzyme: alcohol-dehydrogenase and nicotinamide-adenine-dinucleotide (NAD^+) as a cofactor (see fig. 3.5.1).

Fig.3.5.1



Under influence of aldehyde-dehydrogenase, alcohol is further converted to acetate, in which NAD^+ is reduced again and as a consequence of this, there is enhancement of the $NADH/NAD^+$ ratio in the liver cells, which causes damage to the liver cells (see fig. 3.5.2).

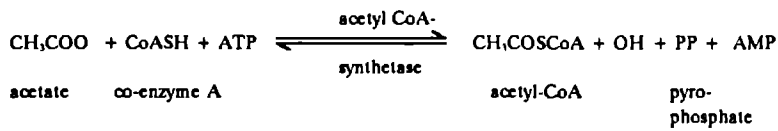
Fig. 3.5.2



NAD^+ is also utilized for the conversion of lactic acid to pyruvic acid, so that the lactic acid/pyruvic acid ratio is enhanced too.

In the mitochondria of the liver cells, acetate with the aid of acetyl-coenzyme A (CoA)-synthetase and ATP is converted to acetyl-coenzyme A (acetyl-CoA) and then oxidized in the citric acid cycle (see fig. 3.5.3).

Fig. 3.5.3



CoA = co-enzyme A

Thiamine pyrophosphate (TPP) is the coenzyme for the transketolase reaction. Besides, it participates as a coenzyme in the oxidative decarboxylation of pyruvate and 2-oxo-glutarate in the citric acid cycle (see fig. 3.5.4 and 3.5.5)

Fig. 3.5.4

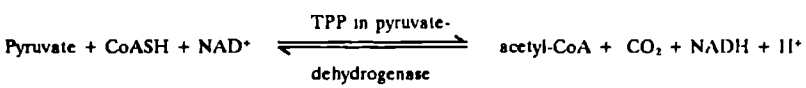
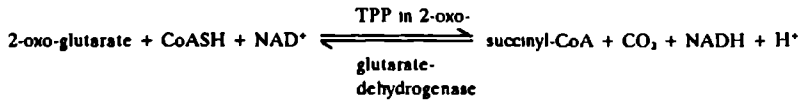


Fig. 3.5.5

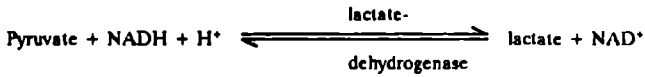


Thiamine deficiency, combined with alcohol-induced deficient NAD^+ enhances the accumulation of pyruvate in blood and tissues This causes an inefficient functioning of the citric acid cycle (see fig. 3.5.4 and 3.5.5).

It is known that thiamine deficiency itself causes inefficient oxidation of the pyruvate. In undernourished alcoholics, there is also disturbance of the elimination of lactic acid by gluconeogenesis.

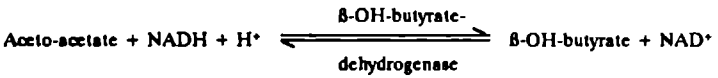
High concentrations of pyruvate and NADH will shift the reaction to the lactate production (see fig. 3.5.6).

Fig. 3.5.6



Moreover, NADH enhances the formation of beta-hydroxy-butyric-acid-acidosis in alcoholics (see 3.5.7).

Fig. 3.5.7



From the above mentioned biochemical reactions, it is concluded, that patients with thiamine deficiency and alcohol abuse are more apt to suffer from shoshin beriberi with severe lactic acidosis than patients with thiamine deficiency caused by insufficient diet alone.

CHAPTER 4

STUDY DESIGN

To determine whether the assumed nutritional polyneuropathy could be ascribed to thiamine deficiency, a prospective study was done of suspected patients, taking into account their living conditions and dietary pattern. An extensive clinical and neurological examination was carried out (Chapter 5).
At the time of the first study (1986-1987), the means to determine blood transketolase activity, thiamine pyrophosphate (TPP) effect or blood thiamine were not yet available. Therefore, the study was repeated in 1989, when these biochemical tests had become available locally.

Apart from dry beriberi, there were also indications that heart failure could be attributed to thiamine deficiency (wet beriberi). Chapter 6 describes the investigations concerning wet beriberi.

Even in the final stages of the above clinical studies, it was still uncertain whether or not biochemical testing for thiamine could be done in Indonesia To prove our assumption that thiamine deficiency per se is the cause of the clinical picture described, an experimental animal study was conducted, in which chickens were fed the type of rice the patients consumed. The procedures followed were those of Eijkman in 1890 (Chapter 7).

To support the results of the clinical studies in polyneuropathic patients, an assessment was made of the existence of marginal, subclinical beriberi polyneuropathy. Relatives of non-polyneuropathic neurological patients and medical and technological students from different income groups were examined, roughly along the same lines as the clinical cases (Chapter 8).

The electrophysiological aspects of beriberi polyneuropathy were examined in a separate study (Chapter 9).

The details of the methodology used are presented in each of the chapters.

CHAPTER 5

BERIBERI POLYNEUROPATHY IN HOSPITAL CASES IN SURABAYA
Incidence, clinical picture and profile of patients

5.1 INTRODUCTION

In a retrospective study of patients with polyneuropathy (PNP) in the period of 1981-1985 an increasing trend was observed towards PNP, which could not be attributed to the common causes of PNP such as diabetes mellitus, uremia, leprosy, Guillain Barré syndrome and toxic PNP (Table 5.1).

TABLE 5.1 INCIDENCE OF NUTRITIONAL POLYNEUROPATHY CASES ADMITTED TO THE NEUROLOGICAL DEPARTMENT, DR. SOETOMO HOSPITAL, SURABAYA, INDONESIA (1981 - 1985)

YEAR	NO. OF PATIENTS	% OF TOTAL ADMISSION
1981	13	13/784 = 1.66 %
1982	12	12/836 = 1.43 %
1983	23	23/975 = 2.36 %
1984	21	21/1010 = 2.08 %
1985	44	44/1015 = 4.33 %
TOTAL	113	113/4620 = 2.44 %

The incidence was highest in the months April through September, and young men were most affected. The majority of the patients belonged to the low income groups. Their diet was monotonous, consisting of large quantities of over-milled rice and little or no good quality food, such as beans, meat, eggs, et cetera.

Clinically, the PNP was characterized by a symmmetrical impairment or loss of motor, sensory and reflex functions. The legs were affected earlier and more severely than the arms, the distal parts being more affected than the proximal ones. The diagnosis of nutritional PNP, probably due to thiamine deficiency, was made. A prospective study was designed to prove the relationship between diet and PNP.

5.2 STUDY DESIGN AND METHODOLOGY

5.2.1 Period August 1986 - August 1987 (Group I)

THIAMIN TETRAHYDROFURFURYL DISULFIDE IN NUTRITIONAL POLYNEUROPATHY (DJOENAIDI AND NOTERMANS, PUBLISHED IN EUR ARCH PSYCHIATR NEUROL SCI 1990;239:218-220).

Subjects

PNP patients, admitted to the Department of Neurology, Dr.Soetomo Hospital, Surabaya, were included in the study if the following criteria were met:

- The patient showed a symmetrical impairment or loss of motor, sensory and reflex functions, usually affecting the legs earlier and more severely than the arms, the distal parts more than the proximal ones.
- Other polyneuropathies, e.g. due to diabetes mellitus, uremia, leprosy, Guillain Barré syndrome and intoxication, were excluded.
- There was a history of nutritional deficiency.
- In electroneuromyography, parameters were indicative of polyneuropathy; for instance, prolonged nerve conduction velocities, denervation activity and reduced interference patterns, especially in the leg muscles, based on the normal values mentioned by Notermans (1984).
- There were no cells or increase of protein in the cerebrospinal fluid.

Examination

For the examination we used special interview and examination sheets, which were to provide information on the following aspects (see Annex 1):

1. Main and additional occupation of all working members of the household
2. Household composition
3. Information on the diet of the family
4. Housing and environmental sanitation
5. History
6. Internal examination
7. Psychiatric examination
8. Neurological examination
9. Electroneuromyographic examination
10. Laboratory examination

Information regarding the patient's main and additional occupation and household composition was gathered by residents of the Department of Neurology, Dr. Soetomo Hospital, Surabaya.

To know the situation of housing and environmental sanitation, house to house visits were performed by a student of statistics of the Institute of Technology, Surabaya, who is acquainted with field surveying.

Data concerning the patient's diet were collected by a nutritionist of the Department of Nutrition of the Dr. Soetomo Hospital.

The interviewing procedure was carried out in three steps. The first step consisted of collecting background information on the patient, such as age, occupation, education, medication, etc. The second step mainly concerned establishing rapport. During this phase, the interviewer introduced him- or herself, explained the purpose of the interview, and tried to create a situation of mutual trust. Step three was data collection. In this stage, the interviewer questioned the patient about food habits. The questions were based on the previously established objectives of the interview.
The patient completed a questionnaire and was asked to recall everything eaten the last 24 hours or the previous day. Significant sources of error were the amount of food eaten; the previous day's intake may have been atypical of the usual intake and the person may not have been telling the truth for a variety of reasons. To overcome some of the weaknesses inherent in the 24-hour recall method, a food frequency

questionnaire was completed. The dietary intake was evaluated by calculating the amounts of the separate nutrients in all food consumed, based on food composition tables.

Internal and psychiatric examinations were carried out by the author. Patients were referred to the Departments of Internal Medicine or Psychiatry, in case of a suspected abnormality.

Residents of the Department of Neurology took the patients' anamneses and did the neurological examinations, later to be checked by the author. To obtain an objective evaluation of their neurological status, all patients were uniformly scored with a modification of Gilroy's scoring (1969). The scoring method allows a maximum of 100 points for a neurologically intact person, distributed as follows :

Normal cranial nerves	20 points
Normal reflexes	18 points
Normal sensory functions	10 points
Normal motor functions	52 points
Total	100 points

This scoring system was devised to express the severity of loss of function. The method is relatively simple and highly reproducible, even if the same patient is scored by different neurologists. The patients were graded as follows: a score of 30-50 meant that the neurological status was poor; a score of 50-70 indicated that it was fair; a score of 70-90 that it was good; and a score of more than 90 indicated an excellent status

Clinical stages

Each patient was classified into one of four distinct categories, according to the severity of the polyneuropathy

Stage I (mild): slight paresis of both dorsal flexors of the feet, the arms are not affected. Ankle jerk is slightly decreased, knee jerk and arm reflexes are normal.

Stage II (moderately severe): moderate paresis of both legs, the arms are slightly affected. Ankle and knee jerks are slightly or moderately decreased, arm reflexes are normal.

Stage III (severe): severe paresis of both legs and mild to moderate paresis of arms. Ankle and knee jerk are non-elicitable, biceps and triceps tendon reflexes are slightly or moderately decreased.

Stage IV (very severe): paralysis of both legs; severe or moderate paresis of both arms. Ankle and knee jerks are non-elicitable, biceps and triceps tendon reflexes are nearly absent or negative.

Motor testing

The power of a muscle or muscle group was graded according to the Medical Research Council (1976) scale:

Grade 5 : complete paralysis (no visible movement)

Grade 4 : flicker or trace of contraction

Grade 3 active movements possible with gravity eliminated

Grade 2 active movements possible against gravity but not against resistance

Grade 1 : active movements possible against both gravity and resistance
Grade 0 : normal power
Grades 1-, 1, and 1+ may be used to indicate movement against slight, moderate and strong resistance.

Sensory testing

Light touch-deep pressure. Light touch-deep pressure testing with monofilaments (von Frey's Semmes-Weinstein monofilaments) of increasing forces has been described as one of the most objective, reproducible tests for measuring cutaneous sensibility, as long as length and diameter of the monofilaments are correct and if the testing is performed according to a standard procedure (Bell, 1985).

The Semmes-Weinstein (S-W) aesthesiometer set used for this study consisted of nylon monofilaments of equal length (35 mm) and varying diameters, fixed into a cut spinal tap needle as a holder. All filaments were calibrated on an analytical balance. Five different filaments of 0.5, 1, 2, 5, and 10 g forces were used. The light monofilaments of 0.5, 1, and 2 g were bounced off the skin three times on the same spot and were bent to exert the specific pressure. The heavier 5 and 10 g filaments were applied only once. All the filaments were applied in ascending (lightest to strongest) order, perpendicular to the skin at an approximate rate of 1 to 1.5 seconds touch, continued in pressure in 1 to 1.5 seconds and lifted in 1 to 1.5 seconds. Subjects were tested in the supine position in a quiet, distraction-free room. Skin temperature was about 32 ° C. The areas of the foot tested were as follows: 1. dorsal between base of hallux and second digit (deep peroneal nerve); 2. at the mid-position of the dorsal foot (superficial peroneal nerve); 3. dorsal at the base of the fifth metatarsal (sural nerve); 4. plantar side at the hallux (medial plantar nerve); 5. plantar: midway above abductor hallucis (medial plantar nerve) and 6. plantar: at the fifth metatarsal head (lateral plantar nerve).
The areas of the hand tested were: 1. palmar side of the thenar (median nerve); 2. palmar side of the hypothenar muscles (ulnar nerve); 3. dorsal: between the first and second metacarpal (radial nerve).
The patient responded yes when a touch was perceived with eyes closed. More than 0.5 g force was interpreted as diminished light touch, more than 1-2 g force as diminished protective sensation and more than 5-10 g force was regarded as loss of protective sensation (Bell, 1985).
Birke and Sims (1986) found 1 g filament as the mean plantar threshold plus two standard deviations for normals and 10 g filament as the level of protective sensation in leprosy patients. In another study, Eko and Djoenaidi (unpublished data) found that at the foot the normal thresholds for sites 1, 2, and 5 and 3, 4, and 6 were 1 g and 2 g, respectively, whereas at the hand the thresholds were 1 g at sites 1, 2, and 3. If 2 or 3 touches were responded to with yes, it was noted as positive, if only 1 touch was felt it was noted as doubtful, and if there was no response at all it was regarded as negative.

Vibration. A 128 cycles-per-second tuning fork with weighted ends was struck against a firm object, following which it was tested on the medial and lateral malleoli of the ankle, tibia, and styloid processes of the radius and ulna. The patient with eyes closed was asked to identify the vibration and to determine when the vibration stopped, the examiner interrupting the vibration at will. In normal young subjects, vibration is felt over the back of the hand for an average of 15 to 20 seconds and over the tibia for

7 to 10 seconds. In patients over 50 years of age, vibration sense is often impaired in the legs (Alpers and Mancall, 1971).

Pain. For testing superficial pain a sharp pin was used. The stimuli were applied first to the hypalgesic area, and from there moved toward the normal parts. The patient was asked to distinguish between the point (sharp sense) and the head of the pin (dull feeling).

Temperature. Temperature sensation was tested by means of test tubes containing cracked ice and hot water. For testing cold, the stimuli should be 5 to 10 °C, and for warmth from 40 to 45 °C (deJong, 1970).

Deep sensibility. To assess the deep sensibility, the sensations of motion and position were tested. In testing, the completely relaxed digits should be grasped laterally with as little pressure as possible, and passively moved. The small toes or fingers were tested first followed by the great toe or thumb. The patient was asked to determine whether the digit was pointing up or down.

Electroneuromyographic examination was done in the private practice of the author during the morning hours, and the results were interpreted by Notermans. For this study, a Medelec MS92 was used. Nerve conduction studies were performed as recommended by Delisa et al. (1987). The H-reflex was judged, using the nomogram of the simultaneous regression of H-wave latency on leg length and age (Delisa et al., 1987). Skin temperature of the appropriate limb was kept constant at a mean value of 33 °C (ranging from 32 ° to 34 °C).

Laboratory examination included electrocardiography, radiography of the chest, blood, blood sugar, liver and kidney function tests, serum total protein and serum albumin. The blood samples were taken immediately to the Department of Clinical Pathology of the Dr. Soetomo Hospital, Surabaya. Cerebrospinal examination was done if considered necessary.

Ex juvantibus proof

All patients were given 2 x 25 mg tetrahydrofurfuryl disulfide (TTFD) intravenously daily for a period of 6 weeks, as treatment in an open trial.

5.2.2 Period January 1989 - December 1989 (Group II)
BERIBERI POLYNEUROPATHY IN LOW INCOME GROUPS

The results of an open trial with thiamine tetrahydro- furfuryl disulfide (TTFD) (ex juvantibus), carried out on patients from low income groups with nutritional polyneuropathy (see 5.2.1), suggested that the polyneuropathy had been caused by thiamine deficiency. Based on the above, this study was conducted. The diagnosis of beriberi polyneuropathy is now supported by blood thiamine determination, a test which has just become available in Surabaya (erythrocyte transketolase testing is still not available).

The aim of this study is to assess the incidence and the cliniconeurological findings of beriberi polyneuropathy in low income group patients who are admitted to the Neurological Department of the Dr. Soetomo Hospital, Surabaya.

Subjects

The subjects were 40 patients with polyneuropathy, admitted to our neurological department. All patients were from low income groups, living on a budget of less than US$ 20.-- a month (ranging from US$ 3.75 to 19.--, or US$ 13.70 ± 5.40)

Examinations

All patients were examined according to a special protocol sheet consisting of anamnesis of household composition, history, internal, psychiatric and neurological examinations (Annex 2), and neurophysiological evaluation (Annex 3). Neuromorphological examination was performed on some of the cases.
Anamneses of household composition and history were taken by residents of the Department of Neurology, of the Dr. Soetomo Hospital in Surabaya.
Internal and psychiatric examinations were performed as described in Chapter 5.2.1.
Neurological examination was simplified. Examination of the motor system consisted of the walk on toes, walk on heels, and squat tests, assessing tenderness of the muscles on palpation, as well as gross examination of the flexors, extensors, adductors and abductors. The grading of muscle strength and weakness was done according to the Clinical Examinations in Neurology of the Mayo Clinic (Aronson et al., 1971) (Annex 2).
Neurophysiological examination is described in Annex 3.
Only few patients gave their consent to undergo a sural nerve biopsy The biopsy was performed by a neurosurgeon of the Department of Neurosurgery, Airlangga University, Surabaya.
Biopsy specimens were fixed in 2 % glutaraldehyde in 0.1 M phosphate buffer at pH 7.4 for two hours. The sural nerve was washed, postfixed in 1 % osmium tetroxide for two hours, dehydrated through ethanol series, and embedded in epon 812. The transverse 1 0 - μm sections were cut with an ultramicrotome, stained with toluidine blue and viewed under light microscopy Teased fibre and electron microscopic studies were not done. The neuromorphological examinations were done by Gabreëls-Festen of the Department of Neurology, neuromorphological section, St Radboud Hospital University Hospital, Nijmegen, the Netherlands
Routine laboratory examination included electrocardiogram, radiography of the chest, haemoglobin, blood glucose, serum creatinine, blood ureum nitrogen, serum glutamic-oxalocytic transaminase, serum glutamic-pyruvic transaminase, serum creatinine phosphokinase (CPK), serum total protein, serum albumin, cerebrospinal fluid and blood thiamine. All specimens were examined at "Prodia" laboratory (a private laboratory), except for blood thiamine.

Indiscriminate prescribing of multivitamins by general practitioners may mask thiamine deficiency. Therefore, all blood thiamine examinations were performed three days after admission to hospital. In the mean time, the patients were given placebo tablets, for instance lactas calcicus.

In the morning before breakfast (after ten hours fasting), 5 ml of blood were drawn by venipuncture into a tube with a 0 25 ml 2% oxalate mixture (3 parts ammonium oxalate and 2 parts potassium oxalate) and prepared for assessment of its thiamine content according to Myint and Houser (1965) It was sent directly to the Department of Biochemistry, Airlangga University, Surabaya

Treatment

All patients were given 2 x 25 mg thiamine tetrahydro-furfuryldisulfide (TTFD) intravenously daily for two weeks, and subsequently 3 x 50 mg TTFD for at least 3 months for therapy.

5.3 RESULTS

a. Characteristics of patients

In the periods August 1986 - August 1987 (group I) and January 1989 - December 1989 (group II), 84 cases of patients with polyneuropathy were admitted to our Neurological Department at the Dr. Soetomo Hospital. They constituted an incidence rate of 39.3/1000 neurological admissions (Table 5.2). Of these patients, 66 were males and 18 were females (ratio 3.7:1). Their ages ranged from 14 to 53 years, with a mean age of 22.7 ± 8.9 years. 77.4% were between 15 and 30 years (Table 5.3), most of them were school children (Table 5.4). The peak incidence occurred from April to September, with fewer cases in January-March and October-December (see Table 5.5).

Fever of unknown cause (32.1%) was the most prevalent precipitating factor, followed by puerperium (7.1%) and alcohol abuse (5.9%). In one case, the patient had taken large amounts of antacids, and in another the disease was brought on by excessive tea consumption (Table 5.6).

All patients were from low income groups and lived on a budget of less than US$ 20.- - a month (ranging from US$ 6.27 to 19.58, or US$ 12.56 ± 5.76). 91.8% were from Surabaya, the remainder from other places in East Java. The number of members of a family ranged from 1 to 11 persons (mean 4.7 ± 2.5). 50% had their own house, 37.5% lived with another family and 12.5% rented a room. 62.5% lived in houses with brick walls, 25% in houses with bamboo walls and floors of cement or soil, 12.5% had walls made of half bricks. The number of rooms ranged from 1 to 5 (mean 2.6 ± 1.4) 87.5% used electricity as the source of light and only 12.5% used oil lamps. Most of them (95%) drank tap water and the remainder indicated wells as their source of drinking water. 87.5% of the patients had their own latrine, while 12.5% disposed of their excreta in the river. 97.6% disposed of their garbage first at public garbage pails from where it is collected by municipal trucks and taken to a garbage dump, 2.4% collected their garbage in garbage holes where they burnt it.

b. Dietary history

Dietary history was registered only in group I. 70% of the patients ate three times a day, 30% ate only twice. Throughout the year, the main food was milled rice, which is distributed by the government. The rice is first cooked and then steamed. To prevent spoiling and a musty smell, the rice is washed until the rice washing is clear. 53.5% of the patients bought cassave (manihot utilisima), talas (taro or colocasia esculenta), or ubi (yam or dioscorea alata) as a complementary food, once or three times a month. The results of the food frequency questionnaire are shown in Table 5.7. Soybean curd or tempe (fermented soya) were consumed by everyone twice or three times a day, but hardly any meat, fish, pulses (such as mung bean or cow pea) and nuts. 66.7% ate sambal as an appetizer (once or twice a day) with vegetables such as Indonesian amaranth, known as "bayam", or swamp cabbage, called

"kangkung" (ipomoea reptans). Eggs were consumed regularly (once or twice a day) by 53.5% of the patients. Based on food composition tables, the amounts of kcal, protein, fat, carbohydrate and thiamine in the previous day's food intake were calculated (24 hours recall). Other vitamins such as riboflavin, pyridoxine and cyanocobalamin could not be calculated since they are not listed in our Indonesian food tables. It seemed that the patients each consumed 1904.5 ± 271.2 kcal, 359 8 ± 99.9 g carbohydrates, 44.1 ± 15.5 g protein, 32.1 ± 27.7 g fat and 0.4 ± 0.2 mg thiamine or 0.21 ± 0.1 /1000 kcal.

c. Neurological signs and symptoms

Numbness or a tingling sensation (92.8%), easy fatigue (80.9%), muscle cramps (70.2%), and cold extremities (54.7%) were the most common complaints. Oedema of the feet and irritability were found in a small percentage of the cases (3.6% and 2.4%, respectively). Anorexia and obstipation were not found (Table 5.8).

Most of the patients (99.2%) came in stages II and III. 54.8% of the cases showed far advanced neurological disturbances resulting in severe paresis with marked muscular atrophy (see Figure 5.1). The legs were more affected than the arms and their distal parts more than the proximal ones. The walk on heels test (92.5% abnormal) proved to be more reliable than squat test (22.5% abnormal)

Involvement of the cranial nerves was found in two cases; one with laryngeal paresis and the other with facial paresis.

The ankle jerks were more severely affected (85.7% absent) than the knee jerks (66.6% absent), while the triceps tendon reflexes (11.9% absent) were more disturbed than the biceps tendon reflexes (5.9% absent). The abdominal and cremaster reflexes were normal (not cited in the table).

Glove-stocking sensation disturbance was found in 60.7% of the cases. Burning paraesthesiae in the feet, as usually found in alcoholic polyneuropathy, were not registered. Touch was mostly affected (leg 88.1%, arm 65.5%), followed by disturbed senses of pain/temperature (leg 75%, arm 60.7%), vibration (leg 61.9%, arm 42.8%), and position (leg 20.2%, arm 10.7%). Hyperaesthesia was found in 4.8% and tenderness of calf muscles in 70.2% of the cases (see Table 5.9)

d. Internal, psychiatric and other abnormalities

Internal, psychiatric and other abnormalities are shown in Table 5.10. Fever of unknown cause was the most prominent feature (32.1%), followed by chronic hepatitis (3 6%), and emotional changes such as irritability (2.4%).

e. Neurophysiological signs

The most abnormal findings in group I were registered in the H-reflexes (100%), in electromyography of the leg muscles (83.3%) and in the distal amplitude of the peroneal nerve (83.3%), followed by the distal amplitude of the posterior tibial nerve (72.2%) and distal amplitude of the sural nerve (55.5%), respectively (see Table 5 11).

In group II, out of all the neurophysiological parameters assessed, decreased distal amplitude of the peroneal motor nerve (96.7%), reduction of the distal amplitude of the H-reflexes (96.8%), and pathologic electromyography in the leg muscles (87.1%) were the most frequently found abnormalities, followed by diminished distal amplitude of the posterior tibial motor nerve (74.2%), decreased distal amplitudes of the sural

nerve (54.8%), median sensory (29%) and median motor nerves (22.6%), respectively (see Table 5.12).
The diagnosis of beriberi polyneuropathy was based on criteria as previously described (Djoenaidi and Notermans, 1990a), and supported by the presence of low blood thiamine levels according to Myint and Houser (1965).

f. Neuromorphological features

Transverse epoxy sections of the sural nerve viewed under light microscopy showed decrease of the density of large myelinated fibres. Endoneurial edema was also noted. Demyelinated axons and myelin ovoids were occcasionally found (fig. 5.2).

g. Laboratory tests

The haemoglobin content, blood sugar, kidney test, serum total protein and serum albumin were all within normal limits. 3.6% showed abnormal serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase. 17.5% of the patients had elevated creatinine phosphokinase. Two patients (2.4%) showed a slight increase in total protein of their cerebrospinal fluids. All patients in group II had low blood thiamine contents: 7.9 ± 1.8 mμg/ml (normal 11.3 - 47.8 mμg/ml. No blood thiamine examinations were done in group I (Table 5.14).
Electrocardiograms and Roentgenograms of the chest showed normal results.

g. Follow up

Group I:
There were 20 patients with severe nutritional polyneuropathy (stage III); 12 were males and 8 were females. Their ages ranged from 14 years to 65 years, with a mean age of 24 years. The mean score on admission was 39 (poor) and after 6 weeks TTFD treatment it had become 59 (fair).
In the moderately severe stage (stage II) there were 18 patients, 9 males and 9 females. Their ages ranged between 15 and 53 years, with a mean of 29.5 years. The initial and final mean scores were 64 (fair) and 75 (good), respectively. Statistical analysis showed that the effect of treatment on the motor functions in stage II and III patients was significant ($p < 0.01$ and $p < 0.05$, respectively), whereas the sensory functions and reflexes did not improve.
There were only 6 patients with mild nutritional polyneuropathy, all of whom were females with a mean age of 22 years. Their mean score on admission was 79 (good) and at the end of the 6th week it had reached 83 (good). Unfortunately, the number of cases was too small for statistical analysis. The outcome of treatment in all the patients is shown in Table 5.15.
On admission all patients were examined electro-physiologically, whereas only 18 patients were re-examined at the end of the trial 6 weeks later (see Table 5.11) The largest percentage of recovery was seen in the electromyogram at voluntary contraction (40%), followed by the motor nerve conduction velocities (peroneal nerve 20%, posterior tibial nerve 15.4%), H-reflexes (16.7%), and sensory nerves (sural nerve 10%). These findings correlate with the clinical outcome. No side effects were observed during TTFD treatment.

Group II:

All patients were followed up neurophysiologically for at least 3 months, because this method of examination is more objective and reliable than neurological examination. All the small hand muscles recovered first, followed by recovery of 95.6% of the gastrocnemial muscles, 96.7% of the peroneal muscles, 86.7% of the deep tendon reflexes, 66.7% of the median sensory nerves, and 70.6% of the sural nerves (see Table 5.12).

5.4 DISCUSSION

It has been proved ex juvantibusly that the cause of nutritional PNP in group I was thiamine deficiency and that all the polyneuropathic patients in group II had low blood thiamine levels.

If we compare the results of groups I and II with those of the patients seen in the period 1981-1985, the following similarities are found. The patients were all from low income groups, and lived on a budget of less than US$ 20 per month, the peak incidence occurred in the months April through September (see Table 5 5), they were of the age group of 15 to 30 years (see Table 5.3); men were more affected than women (see Table 5.3); their diets were monotonous, with large quantities of steamed milled rice, hardly any meat, fish, pulses or nuts (see Table 5.7).
It seems therefore likely that the nutritional PNPs in 1981-1985 were also caused by thiamine deficiency.

All patients consumed machine-milled rice, which is distributed by the Indonesian Government. It is stored for a long time and sometimes in humid places so that a loss in thiamine is likely. Samples of 3 types of uncooked polished rice, sold at the market in Surabaya, had an average thiamine content of 0.134 mg per 100 g rice (unpolished rice contains 0.32 mg per 100 g). Distributed government rice had a thiamine content of 0 125 mg per 100 g rice (Djoenaidi, unpublished data). Dawiesah (1983) in Yogyakarta, Indonesia, found 0.126 ± 0.043 mg thiamine in 18 samples of 100 g polished rice, whereas Munger and Booton (1990) found 0.115 ± 0.01 mg thiamine per 100 g rice in Phanat Nikhom in 1988.

Analysis of the previous day's intake of food (using food tables) of our nutritional PNP patients revealed that the thiamine intake was 0.4 ± 0.2 mg per 1904.5 ± 271.2 kcal or 0.21 ± 0.1 mg per 1000 kcal. In South China, Chen et al. (1984) found that the average intake of thiamine was 0.24 mg/1000 kcal in patients with beriberi, and suggested that 0.5 mg/1000 kcal might be recommended as the dietary thiamine requirement. The minimum thiamine intake according to the WHO standard (1976) is 0.4 mg/1000 kcal.

Assessment of blood thiamine levels in group II showed low blood thiamine contents: 7.9 ± 1.8 mμg/ml (normal 11.3-47.8 mμg/ml).

Analysis at random (using food tables) of our neurological ward diets, revealed that 76.4% (3325.53 g carbohydrate) of the 1740.33 kcal were from carbohydrates (mainly steamed milled rice), 11.03% (21.33 g fat) and 12.54% (54 56 g protein) were from fat and protein, respectively. The thiamine content was 0.506 mg or 0.3 mg/1000 kcal. We may conclude that the improvement of our beriberi PNP patients was not due to the hospital diets.

Washing the rice until the rice washing is clear, which is usually done at home to prevent a stale and musty smell of the rice, appears to be the main cause of thiamine loss. Alejo et al. (1954) found a washing loss of 18 85% for thiamine in ordinary polished rice and an average of 35% (range 26.92 to 48.46%) thiamine loss in

cooking. It is estimated that about 85% of the thiamine is lost by discarding the water after soaking and boiling the rice (Tmangraksatve, 1955). Dawiesah (1983) found a loss of 55.04% thiamine in washing the rice three times, rubbing it twice and then cooking it, whereas only 16 4% thiamine is lost after washing twice, rubbing once, and cooking. Chen et al. (1984) showed that as much as 20% of thiamine is lost in the Chinese method of washing the rice several times before cooking.

Vegetables such as Indonesian amaranth (Table 5.7) which are often consumed at home, have an antithiamine activity. This may add to the thiamine deficiency.

The incidence rate of beriberi PNP in groups I and II was 3.9% of the total neurological admissions. This is almost the same as in 1985 (4.3%) It is estimated that the incidence rate is in reality larger, since mild cases and very poor patients may not be seen in the hospital at all. They go to practicing nurses or to a medicine man (called "dukun"), or they buy traditional medicine in small shops. There are very few community-based studies of beriberi PNP reported from Africa and Asia In a population study in Africa, Osuntokun (1984) found a prevalence rate of symmetrical PNP of 7 per 1000. Wadia (1984) reported that 41 8% of 67 malnourished patients, who were admitted to a teaching hospital in Bombay, had peripheral sensory neuropathy, probably caused by thiamine or multivitamin B deficiency Chen et al (1984) found a 34% incidence of beriberi among 116 peasants of 30 families who discarded the water in which the rice was cooked, instead of using it for consumption

In our study, men (78.5%) were more affected than women, with a peak age of incidence between 15 and 30 years. Chen et al. (1984) also found a male preponderance (63.9%) with an age distribution between 15 and 44 years. Mengistu and Maru (1979) reported that all cases of dry beriberi were of young males with a mean age of 23.5 years (ranging from 18 to 50 years) Eijkman (1927) found in a study with experimentally induced beriberi in chickens, that cocks were more apt to suffer from beriberi than hens, and that cockerels (non-adult) were more prone to have this disease than cocks (adult). It seems a likely conclusion that males are physically more active than females and need more thiamine. The more carbohydrate-rich food is consumed, the greater the thiamine requirement. The staple diet of our low income beriberi polyneuropathic patients consisted mainly of carbohydrates, especially steamed milled rice.

In human beriberi there is a marked seasonal difference. Our beriberi polyneuropathic patients most often presented in the months of April through September, so during the transition of wet to dry and dry seasons. High environmental temperatures and humidity seem to influence the need for thiamine In Japan, beriberi is most prevalent in summer and autumn (Shimazono J, 1962) Chen et al (1984) found that in China the incidence of beriberi markedly increased in April, while the peak was reached in May.

Fever of unknown cause (32.1%) (table 5.6), which subsided without treatment within 24 hours of admission, was the most common precipitating cause in our beriberi polyneuropathic patients It seems that the need for thiamine increases with conditions such as fever, malaria and physical exertion (Everett, 1979) Mengistu and Maru (1979) reported that malaria, high atmospheric temperatures of up to 46 °C, and fever of unknown cause were the factors involved in the causation of dry beriberi in North-West Ethiopia. In one case, the cause of beriberi polyneuropathy was chronic use of antacids (table 5 6). It was found that magnesium trisilicate absorbs relatively large amounts of thiamine, consequently chronic use of it may impair the intestinal absorption of thiamine (Borst, 1980) In another case (table 5 6) it was caused by drinking large amounts of tea. The antithiamine activity of tea appeared

to be related to its tannin content (Hilker et al., 1974). 5.9% of our beriberi polyneuropathic cases were caused by alcohol abuse (table 5.6). Alcohol inhibits glucose transport across the brush border membrane and it depresses the membrane-bound enzymes (Hoyumpa et al., 1981). Besides, alcohol interferes with the active gastrointestinal transport of thiamine. Alcohol is also a rich source of non-nutritive calories, so that heavy drinking is often complicated by malnutrition and vitamin deficiency other than thiamine (Charness et al., 1989; Thomas, 1986). Alcohol also damages the liver cells, so that activation of thiamine pyrophosphate from thiamine is decreased and the capacity of the liver to store thiamine is diminished (Majoor and Hillen, 1982; Reuler et al., 1985). Inherited abnormality of thiamine-dependent transketolase, which reduces its affinity for thiamine, is found in some individuals (Blass and Gibson, 1977). Anorexia, diarrhea and obstipation were not found in our cases. Shimazono (1962) said that polished rice causes diarrhea in man, but human avitaminosis has a tendency to constipation. Marked anorexia, nausea and vomiting are always present in avitaminosis. They are not seen in ordinary beriberi, only in cases of acute pernicious beriberi (shoshin) they may be present. On the other hand, Chen et al. (1984) reported that anorexia and general malaise associated with heaviness and weakness of the legs were the early symptoms of beriberi polyneuropathy.

Vagus nerve involvement was found in one case, and in another (table 5.9) there was facial paresis. Other cranial nerves were not affected. Deafness, numbness around the lips, weakness of the tongue, bilateral facial weakness, and blindness have all been noted in rare instances of polyneuropathy due to nutritional deficiency and alcoholism (Victor, 1984).

The distal muscles were more affected than the proximal muscles and their distal segments more than the proximal ones. Failure of axon transport results in degeneration of vulnerable distal regions of long superficial or large diameter axons. Degeneration appears to advance proximally towards the cell body (dying back), as long as the metabolic abnormality persists (Schaumburg et al., 1983).

The Semmes-Weinstein (S-W) monofilament testing seemed to be more sensitive than routine sensibility testing, but less sensitive than neurophysiological examination. The sensitivity of S-W tests to electroneuromyography was 65.8% and the specificity 80%, whereas in routine sensibility testing, sensitivity and specificity were 30.76% and 100%, respectively (Eko and Djoenaidi, unpublished data). In the legs, 88.1% of the cases had a deviating S-W test, whereas 61.9% and 20.2% of these cases had abnormal results in vibration and position sense testing, respectively (see Table 5.9). The S-W monofilament testing, which evaluates the slowly adapting fibres, seemed more sensitive than the vibration tests, which evaluate the quickly adapting fibres. A slowly adapting fibre continues its pulse response throughout the duration of the stimulus, whereas a quickly adapting fibre signals an on-off event (Gelberman et al., 1983). Position sense is less reliable; it requires complex overlapping and intermingling of different sensory units, as well as a great deal of cortical integration. Only 4.8% of our beriberi polyneuropathic patients showed hyperaesthesia (table 5.9). Burning paraesthesiae in the feet were not found. It seemed that our patients suffered from chronic forms of nerve fibre degeneration. Neuropathic painfulness of the feet was found to be related to the rate and kind of nerve fibre degeneration. Patients with acute breakdown of myelinated fibres (either by Wallerian or axonal degeneration) tend to have pain more often and to a greater degree than do patients with a more chronic form of nerve fibre degeneration. Neuropathic painfulness was not found to be related simply to the ratio of remaining large and small fibres after nerve fibre degeneration (Dyck et al., 1976).

Abnormal reflexes are the most sensitive indicator of polyneuropathy. 89.7% and 5.6% of our patients showed non-elicitable ankle and knee jerks (see Table 5.9). In xonal neuropathy the large motor (efferent) fibres conducted normally, whereas owing of velocity was observed in the Ia afferent fibres (Blackstock et al., 1972).

Profuse sweating was found in some patients (19.1%) (table 5.8). This abnormality iay be due to involvement of the peripheral (postganglionic) sympathetic efferent erve fibres.

Abnormal H-reflexes are frequently one of the earliest signs of polyneuropathy Notermans, 1984). 100% of group I and 96.8% of group II patients showed bnormal H-reflexes with prolonged interval latency time and low amplitude. In :vere cases they were non-elicitable.

Abnormalities of the electromyogram were found in 83.3% of the cases in group , (table 5.11) and in 87.1% in group II (table 5.13). They consisted of fibrillation otentials, positive sharp waves and increased insertion activity in the distal small and and foot muscles. Sometimes fasciculations were seen. The interference pattern /as reduced during maximal effort and in severe cases there were only single motor nit potentials. The duration of the motor unit action potentials was prolonged and ieir amplitudes were higher. In mild cases, an increase in the percentage of olyphasic muscle action potentials was found.

In metabolic nutritional neuropathy, the sensory nerves are affected earlier than the iotor nerves, especially in the lower extremities. The sensory nerve action potentials f the sural nerve are more commonly and severely affected than the motor nerve ction potentials (Lefebvre et al., 1979). This is in contrast with our findings; of our ases 55.5% (group I) (table 5.11) and 54.8% (group II) (table 5.12) showed bnormalities of the sural nerve action potentials, whereas in 83.3% (group I) and 6.7% of the cases a reduction of the distal amplitudes of the peroneal nerves was ound (table 5.11 and 5.12).

In mild cases there was a slight reduction in the conduction velocity, but not below 0% of normal. In general, there was a progressive reduction in amplitude and lispersion of the evoked response on distal stimulation. In severe cases there was a ironounced slowing of conduction or even failure to evoke a response. The primary esion in nutritional polyneuropathy is one of axonal degeneration, the myelin changes ieing secondary (Victor, 1984).

In our trial (group I) we found that the improvements of motor function were tatistically significant, whereas the reflexes and sensory functions did not improve ignificantly (see Table 5.15). These data were in accordance with the neurophysio-ogical findings, in which the largest percentage of improvements was established in he electromyogram, followed by improvements of the motor nerve conduction elocities, H-reflexes and sensory nerves, respectively (see Table 5.11). It seems likely hat spindle afferent fibres, which induce the monosynaptic reflex via the sensory erves, are more vulnerable than the motor nerves. Tables 5.12 and 5.13 show that he abnormal findings in group II began in the distal regions moving towards the iroximal ones, the legs being more affected than the arms. In recovery the order was eversed, i.e. the proximal arm muscles recovered first, followed by the distal astrocnemial and peroneal muscles. It seems that in beriberi polyneuropathy the legeneration advances proximally toward the cell body (dying back), and that ecovery takes place from proximal to distal

n some severe cases, followed up for more than one year, there was no complete ecovery. The dorsiflexors of the feet remained weak, the Achilles jerks were absent, nd the tingling sensation was still present. Apparently, recovery of distal (dying back) xonopathy in severe beriberi is poor, and in very severe cases the symptoms persist,

although patients are given multivitamins and mineral supplements. Gill and Bell (1982) reported that although nutritional neuropathy disappeared soon after release in most ex-Far East prisoners of war, in some they have persisted up to 36 years since exposure to the nutritional insult. This persistent neuropathy is likely to be due to central distal axonopathy (extensive degeneration of the distal ends of fibres in the posterior columns) (LeQuesne, 1983).

In our case, transverse epoxy sections of sural nerve biopsy specimens viewed under light microscopy showed marked decrease of the density of the large myelinated fibres and endoneurial edema. Myelin ovoids and demyelinated axons were occasionally found (fig.5.2).

In beriberi neuropathy Ohnishi et al. (1980) found marked reduction of the large myelinated fibres, with preservation of the density of small myelinated and unmyelinated fibres. In teased fibre analysis segmental demyelination was very uncommon. Alteration of the myelin sheath without concomittant lesions of the axon were rare. Linear rows of myelin ovoids were less frequently observed.

Takahashi and Nakamura (1976) found nonspecific axonal lesions with accumulations of flattened sacs or tubules in the axoplasm of large myelinated fibres. These particular features were also described by Prineas (1970) in thiamine-deficient rats. These authors have suggested that the rare signs of segmental demyelination could be secondary to axonal degeneration.

All of our patients had normal serum total protein, serum albumin and haemoglobin levels (Table 5.14). It is suggested that malnutrition is not an important factor in the pathogenesis of beriberi in Indonesia. The creatinine phosphokinase (CPK) was elevated in 17.5% (mean 132.57 ± 37.3 units) of the cases (Table 5.14), indicating a disturbance of the metabolism of the muscles. De Bruijn and Keyser (unpublished report, 1988) found 29% enhanced CPK in thiamine-deficient patients who were admitted to the neurological department of the St. Radboud University Hospital, Nijmegen. Three cases of our patients showed abnormal liver function tests, probably caused by chronic alcohol abuse or chronic liver disease (table 5.14).

5.5 SUMMARY

The beriberi PNPs in this prospective study seemed to have the same pattern of age, sex, seasonal distribution and dietary history as found in nutritional PNP patients during the period of 1981-1985. They were from low income groups. In 1986-1987, the diagnosis of beriberi PNP was made ex juvantibusly, as biochemical tests were locally unavailable. In 1989, the diagnosis was supported by the low blood thiamine levels and the dramatic response to TTFD.

The incidence rate of beriberi polyneuropathy among low income groups is estimated at around 40/1000 neurological admissions.

Men were more affected than women, with a peak age of incidence between 15 and 30 years. It was most prevalent in the transition of wet to dry and dry seasons. Fever of unknown cause, which subsided without treatment, was the most common precipitating cause. Malnutrition is not an important factor in the pathogenesis of beriberi polyneuropathy in Indonesia. Tingling sensations, easy fatigue, and muscle cramps were the most common complaints and antedated many years before the polyneuropathic attack. Disturbances of reflexes, touch sensation, and motor functions were the most abnormal neurological signs. The cranial nerves were rarely involved. Cerebrospinal fluid was normal. A modest elevation in protein was present in some advanced cases. The legs were more affected than the arms, and their distal segments

more than the proximal ones. The recovery of the muscles took place in the reverse direction i.e from proximal to distal. In severe cases, the recovery was poor.
Electromyography, nerve conduction abnormalities and neuromorphological features were typical of axonal degeneration and support the notion that beriberi PNP represents a distal axonopathy.
It appears that beriberi occurs more frequently than expected and it is usually not diagnosed clinically as such.
Community based surveys are recommended to assess the prevalence of thiamine deficiency.

TABLE 5.2 INCIDENCE OF BERIBERI POLYNEUROPATHY

MONTH/YEAR	NO. OF PATIENTS	% OF TOTAL ADMISSIONS
8/1986 - 8/1987	44	44/1093 = 4.03%
1/1989 -12/1989	40	40/1044 = 3.83%
TOTAL	84	84/2137 = 3.93%

TABLE 5.3 AGE AND SEX DISTRIBUTION

AGE RANGE (YEARS)	GROUP I SEX		GROUP II SEX		% OF TOTAL
	MALE	FEMALE	MALE	FEMALE	
< 15	-	-	-	2	2.4
15 - 30	26	6	28	5	77.4
31 - 50	6	3	3	2	16.6
51 or older	3	-	-	-	3.6
Total	35	9	31	9	
Mean age	23.4	23.7	21.3	23.4	22.7
SD	10.7	6.9	6.1	11.6	8.9

TABLE 5.4 OCCUPATION

OCCUPATION	GROUP I	GROUP II	% OF TOTAL
SCHOOL CHILDREN	24	25	58.3
STUDENTS	-	2	2.4
UNEMPLOYED	6	4	11.9
EMPLOYED	14	9	27.4
TOTAL	44	40	

TABLE 5.5 SEASONAL DISTRIBUTION OF ADMITTANCE

MONTH	GROUP I	GROUP II	% OF TOTAL
JANUARY - MARCH (WET SEASON)	5	7	14.3
APRIL - JUNE (TRANSITION WET-DRY)	21	16	44.0
JULY - SEPTEMBER (DRY SEASON)	15	14	34.5
OCTOBER - DECEMBER (TRANSITION DRY-WET)	3	3	7.2
TOTAL	44	40	

TABLE 5.6 PRECIPITATING FACTORS

PRECIPITATING FACTORS	NUMBER OF PATIENTS GROUP I	GROUP II	% OF TOTAL
FEVER OF UNKNOWN CAUSE	13	14	32.1
ALCOHOL ABUSE	1	4	5.9
ALLERGY	-	2	2.4
PREGNANCY	-	1	1.2
PUERPERIUM	6	-	7.1
OTITIS MEDIA CHRONICA	-	1	1.2
CHRONIC HEPATITIS	2	1	3.6
ANTACIDS	-	1	1.2
MOUNTAIN CLIMBING	-	1	1.2
EXCESSIVE TEA CONSUMPTION	-	1	1.2
UNKNOWN	22	15	44.0

TABLE 5.7 DIETARY HISTORY

ITEM	PERCENTAGE	ITEM	PERCENTAGE
SERVINGS		**SIDE DISHES**	
3 x a day	70	fish	
2 x a day	30	< 3 x a week	47.7
		never	53.5
		eggs	
COMPLEMENTARY FOOD		1-2 x a day	53.5
cassave/taro/yam		< 3 x a week	33.2
1-2 x a month	53.3	never	13.3
never	46.7	sambal	
		1-2 x a day	66.7
		< 3 x a week	20.0
SIDE DISHES		never	13.3
bean curd/tempe		vegetables	
2-3 x a day	100	Indon. amaranth (bayam)	
pulses or nuts		swamp cabbage (kangkung)	
1-2 x a month	40	mustard greens (sawi)	
never	60	1-2 x a day	46.7
meat		3-4 x a day	53.5
1-2 x a month	86.7		
never	13.3		

TABLE 5.8 ABNORMAL NEUROLOGICAL SYMPTOMS

SYMPTOMS	NO. OF ABNORMALITY GROUP I	GROUP II	% OF TOTAL ABNORMALITY	DURATION OF SYMPTOMS RANGE (MEAN / DAYS)
NUMBNESS/ TINGLING FEELING	40	38	92.8	1 WK-2 YRS (193.6 ± 233.42)
EASY FATIGUE	36	32	80.9	1 WK-3 YRS (149.34 ± 242.12)
MUSCLE CRAMPS	28	31	70.2	1 WK-3 YRS (304.9 ± 309.63)
COLD EXTREMITIES	21	25	54.7	1 WK-1 YR (69.88 ± 97.36)
PROFUSE SWEATING	9	7	19.1	1 WK-4 MO (53.86 ± 48.38)
OEDEMA (ANKLES)	1	2	3.6	-
IRRITABILITY	-	2	3.6	-
ANOREXIA	-	-	-	-
OBSTIPATION	-	-	-	-

WK = Week ; YR = year ; MO = month ; NO. = number

TABLE 5.9 ABNORMAL NEUROLOGICAL SIGNS

STAGE/SIGNS	NO.OF ABNORMALITY GROUP I	GROUP II	% OF TOTAL ABNORMALITY
CLINICAL STAGE I	: 6	3	10.7
II	: 18	11	34.5
III	: 20	26	54.8
Squat test	: NOT DONE	9	22.5
Walk on heels	: NOT DONE	37	92.5
Walk on toes	: NOT DONE	26	65
CRANIAL NERVES			
Laryngeal paresis	: -	1	1.2
Facial paresis	: 1	-	1.2
SENSORY FUNCTION			
Legs			
S-W test	: 40	34	88.1
Pain/temperature	: 33	30	75
Vibration	: 28	24	61.9
Position	: 10	7	20.2
Arms			
S-W test	: 29	26	65.5
Pain/temperature	: 27	24	60.7
Vibration	: 19	17	42.8
Position	: 5	4	10.7
Hypersensitive	: -	4	4.8
Glove-stocking	: 27	24	60.7
Tenderness of calf muscles	: 31	28	70.2
REFLEXES			
Legs			
Ankle jerk			
absent	: 39	33	85.7
reduced	: 5	4	10.7
Knee jerk			
absent	: 30	26	66.6
reduced	: 14	11	29.8
Arms			
Biceps jerk			
absent	: 3	2	5.9
reduced	: 30	24	64.3
Triceps jerk			
absent	: 6	4	11.9
reduced	: 27	24	60.7

S-W = Semmes-Weinstein

TABLE 5.10 INTERNAL, PSYCHIATRIC AND OTHER ABNORMALITIES

DISEASE	NO. OF ABNORMALITY GROUP I	GROUP II	% OF TOTAL ABNORMALITY
FEVER ET CAUSA IGNOTA	13	14	32.1
CHRONIC HEPATITIS	2	1	3.6
PEPTIC ULCER	0	1	1.2
DERMATITIS	0	1	1.2
CHRONIC OTITIS MEDIA	0	1	1.2
IRRITABILITY	0	2	2.4
	15	20	41.7

TABLE 5.11 ELECTROPHYSIOLOGICAL FINDINGS BEFORE AND AFTER TREATMENT WITH TTFD (18 PATIENTS) (GROUP I).

PROCEDURE	ON ADMISSION NO. OF ABNORMAL CASES	AFTER TREATMENT NO. OF IMPROVED CASES
H-REFLEX	18 (100%)	3 (16.7%)
AMPLITUDE DISTAL LATENCY		
Peroneal nerve	15 (83.3%)	3 (20%)
Post.tib.nerve	13 (72.2%)	2 (15.4%)
Median nerve	3 (16.7%)	1 (33.3%)
Ulnar nerve	0	0
SNAP		
Median nerve	6 (33.3%)	2 (33.3%)
Ulnar nerve	4 (22.2%)	0
Sural nerve	10 (55.5%)	1 (10%)
E M G (anterior tibial)	15 (83.3%)	6 (40%)

MCV = Motor nerve conduction velocity;
SNAP = Sensoric nerve action potential.

TABLE 5.12 ELECTRONEUROGRAPHIC FINDINGS BEFORE AND AFTER TREATMENT (GROUP II)

NERVES/H-REFLEX	PERCENT ABNORMALITY	MEAN ABNORMALITY	PERCENT RECOVERY (I-N)	MEAN RECOVERY	NORMAL VALUE
PERONEAL MOTOR					
Latency time					
ankle	87.1	7.34 ± 1.84 msec	96.3 (53.8-46.2)	5.5 ± 0.91 msec	3.77 ± 0.62 msec
knee	67.7	16.49 ± 3.25 msec	90.5 (36.8-63.2)	12.69 ± 2.18 msec	10.79 ± 1.06 msec
Amplitude					
ankle	96.7	659.83 ± 1117.48 UV	96.7 (89.7-10.3)	2153.62 ± 2514.66 UV	5100 ± 2300 UV
knee	93.5	656.21 ± 1183.63 UV	96.5 (92.9- 7.1)	1904.29 ± 2433.4 UV	5100 ± 2000 UV
MCV	64.5	27.89 ± 17.79 m/sec	90.0 (38.9-61.1)	44.63 ± 9.09 m/sec	52.6 ± 3.8 m/sec
POSTERIOR TIBIAL MOTOR					
Latency time					
ankle	51.6	5.85 ± 1.39 msec	87.5 (35.7-64.3)	4.64 ± 1.13 msec	3.86 ± 0.6 msec
knee	22.5	17.93 ± 5.68 msec	85.7 (50.0-50.0)	14.6 ± 2.15 msec	12.05 ± 1.5 msec
Amplitude					
ankle	74.2	2370.22 ± 24441.0 UV	95.6 (54.6-45.4)	6338.66 ± 4223.79 UV	5800 ± 1900 UV
knee	70.9	2005.23 ± 1828.02 UV	95.4 (66.7-33.3)	5126.19 ± 3235.64 UV	5100 ± 2200 UV
MCV	16.1	25.88 ± 16.89 m/sec	80.0 (50.0-50.0)	41.95 ± 7.92 m/sec	47.2 ± 3.6 m/sec
MEDIAN MOTOR					
Latency time					
wrist	12.9	5.5 ± 1.65 msec	100.0 (25.0-75.0)	4.4 ± 1.27 msec	3.49 ± 0.34 msec
elbow	6.4	13.9 ± 5.23 msec	100.0 (100 - 0)	11.3 ± 2.69 msec	7.39 ± 0.69 msec
Amplitude					
wrist	22.6	2928.57 ± 1693.83 UV	100.0 (42.9-57.1)	8857.14 ± 3436.49 UV	5100 ± 3000 UV
elbow	19.3	2583.33 ± 1562.58 UV	100.0 (50.0-50.0)	6833.33 ± 4308.91 UV	5100 ± 2700 UV
MCV	6.4	32.7 ± 18.24 m/sec	100.0 (50.0-50.0)	41.95 ± 21.28 m/sec	57.7 ± 3.8 m/sec
SURAL SENSORY (ORTHODROMIC)					
Distal latency	48.3	3.41 ± 0.26 msec	80.0 (33.3-66.7)	2.8 ± 0.45 msec	2.08 ± 0.35 msec
Amplitude	54.8	1.06 ± 1.15 UV	70.6 (58.3-41.7)	4.34 ± 2.7 UV	5 UV
MEDIAN SENSORY (ORTHODROMIC)					
Distal latency	12.9	NIHIL	50.0 (100 - 0)	3.48 ± 1.19 msec	2.84 ± 0.34 msec
Amplitude	29.0	4.33 ± 4.3 UV	66.7 (16.7-83.3)	13.17 ± 5.91 UV	10 UV
H-REFLEX (M.SOLEUS)					
Latency time	83.9	33.38 ± 3.07 msec	80.8 (100-0)	31.74 ± 2.5 msec	25.8 ± 1.8 msec
Amplitude	96.8	298.83 ± 625.11 UV	86.7 (100-0)	909.61 ± 937.79 UV	112381 ± 409.6 UV

MCV = motor conduction velocity
I = % improved cases
N = % normal cases

TABLE 5.13 ELECTROMYOGRAPHIC FINDINGS BEFORE AND AFTER TREATMENT (GROUP II)

MUSCLE	POSITIVE SHARP WAVE		FIBRILLATION POTENTIAL		REDUCED CMAP	
	% ABNORMALITY	% RECOVERY (I - N)	% ABNORMALITY	% RECOVERY (I - N)	% ABNORMALITY	% RECOVERY (I - N)
Anterior tibial	87.1	77.8 (61.9-38.1)	54.8	94.1 (12.5-87.5)	96.8	90 (81.5-18.5)
A P.B.	41.9	100.0 (53.9-46.1)	22.6	100.0 (28.6-71.4)	41.9	100 (38.5-61.5)

CMAP = compound muscle action potential
A P.B. = abductor pollicis brevis
I = % improved cases
N = % normal cases

TABLE 5.14 LABORATORY FINDINGS

ITEM	TOTAL MEAN VALUE		NO.OF ABNORMAL PATIENTS		ABNORMAL (% OF TOTAL)	NORMAL CONVENTIONAL UNITS
	GROUP I	GROUP II	GROUP I	GROUP II		
HAEMOGLOBIN	13.7 ± 1.4	13.95 ± 1.83	0	0	0	12 - 18 GRAMS/DL
BLOOD GLUCOSE						
FASTING	78.8 ± 8.4	75.21 ± 10.57	0	0	0	< 115 MG/DL
2 HOURS POST PRANDIAL	106.7 ± 7.2	104.6 ± 6.2	0	0	0	< 140 MG/DL
SGOT	26.7 ± 11.9	24.78 ± 14	2	1	3.6	7 - 40 MILLIUNITS/DL (37° C)
SGPT	26.6 ± 14.3	23.14 ± 18.45	2	1	3.6	5 - 35 MILLIUNITS/DL (37° C)
CREATININE (SERUM)	1.01 ± 0.1	0.97 ± 0.23	0	0	0	0.6 - 1.2 MG/DL
UREA (BLOOD)	15.6 ± 4.3	14.12 ± 4.73	0	0	0	21 - 43 MG/DL
CREATININE PHOSPHOKINASE (CPK)	NOT DONE	70.42 ± 41.03	NOT DONE	7	17.5	10 - 80 UNITS (30°C)
TOTAL PROTEIN (SERUM)	7.2 ± 0.5	7.27 ± 0.98	0	0	0	6 - 8 GRAMS/DL
ALBUMIN (SERUM)	4.4 ± 0.5	4.31 ± 0.54	0	0	0	3.5 - 5.5 GRAMS/DL
THIAMINE (BLOOD)	NOT DONE	7.9 ± 1.8	NOT DONE	40	100	11.3 - 47.8 mμG/ML (Myint & Houser, 1965)
CEREBROSPINAL FLUID :						
CELLS	1.9 ± 1.2	2.52 ± 1.73	0	0	0	< 5/CU MM;ALL MONONUCLEAR
PROTEIN,TOTAL	21.2 ± 15.1	23.78 ± 10.23	1	1	2.4	15 - 45 MG/DL

SGOT = SERUM GLUTAMIC-OXALOACETIC TRANSAMINASE
SGPT = SERUM GLUTAMIC-PYRUVIC TRANSAMINASE

TABLE 5.15 OUTCOME OF TREATMENT WITH TTFD (GROUP I).

	NO.OF PATIENTS	SUMMATED SCORE	NO.OF IMPROVED PATIENTS	SUMMATED SCORE	P (WILCOXON)
CRANIAL NERVES	44	880	-	880	-
REFLEXES	44	112	7	170	$p < 0.1$
SENSORY FUNCTIONS	44	290	9	329	$p < 0.1$
MOTOR FUNCTIONS	44	1144.5	34	1674	$p < 0.01$
TOTAL SCORE		2426.5		3053	$p < 0.01$
MEAN SCORE		55.1 (FAIR)		69.4 (GOOD)	

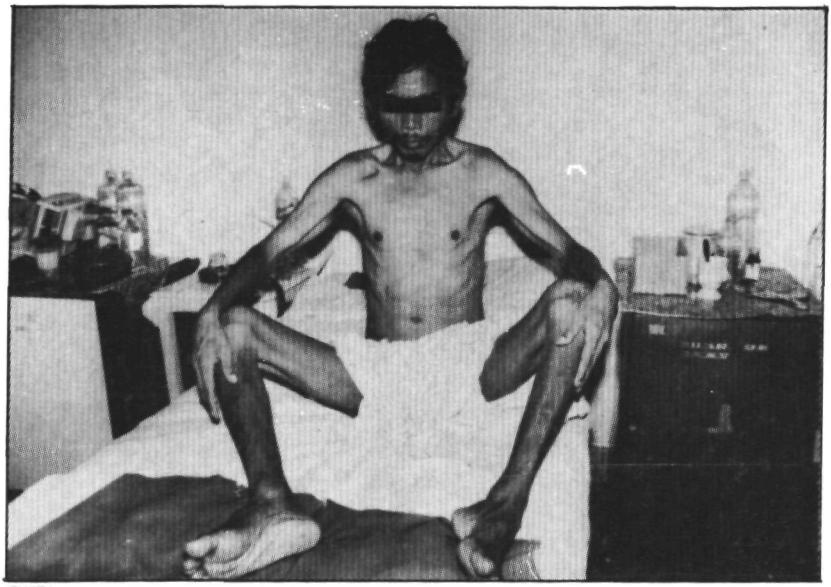


Fig.5.1 A 37-year-old man with severe beriberi polyneuropathy (dry beriberi)

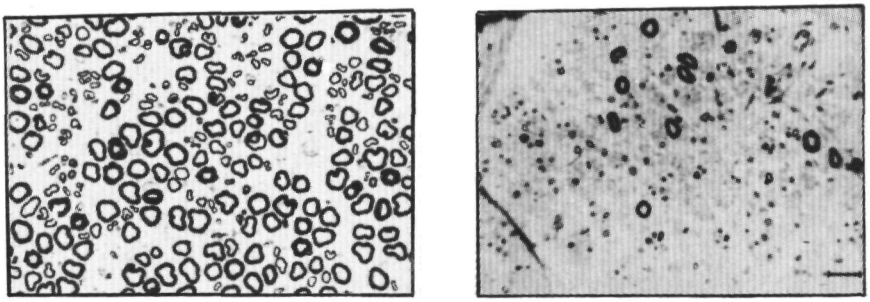


Fig. 5.2 Transverse epoxy sections of sural nerve in control (left) and severe beriberi polyneuropathy (case fig. 5.1, right). Note decrease of the density of large myelinated fibres and endoneurial edema. Toluidine blue staining, x 142, bar = 18 μm.

CHAPTER 6

BERIBERI CARDIOMYOPATHY
(Djoenaidi, Notermans and Dunda)
(submitted to European Journal of Clinical Nutrition)

6.1 INTRODUCTION

The term beriberi is derived from the Singhalese word beri meaning "I cannot". The result of thiamine deficiency is a spectrum of conditions, classically divided into two major types - dry beriberi, in which the features of peripheral neuropathy predominate, and wet beriberi, which presents with the symptoms and signs of cardiac failure. Cardiac beriberi is arbitrarily divided into the acute fulminant form (shoshin beriberi) and the chronic type (Wolf and Levin, 1960).

In Indonesia, Thailand, and the Philippines beriberi appears to be endemic where the diet consists mainly of polished or milled rice, from which the tiny silver scales containing thiamine have been removed (Djoenaidi et al. 1990). In the West this disease is reported in association with chronic alcoholism (Notermans et al., 1990).

6.2 CASE REPORTS

Case (I) A 21-year-old student was admitted to the intensive coronary care unit of the Dr. Soetomo Hospital in Surabaya, Indonesia, with severe respiratory distress. He had been addicted to alcohol for 4 years, and in the last 3 weeks his alcohol consumption had been extremely high, while his diet consisted of junk food (3 x Rp 500 [=US$ 0.84 a day]). Three years before admission he already had complaints of muscle cramps, numbness of the extremities and of being easily fatigued. Three days before being admitted to the hospital, he developed a sudden severe dyspnea, two-pillow orthopnea, paroxysmal nocturnal dyspnea with cough, fever, anorexia and intermittent nausea and vomiting.

Physical examination showed a well developed, moderately well nourished man, who was somnolent with severe respiratory distress. The hands and feet were cold and cyanotic. There was no nystagmus, nor paresis of the eye muscles. The cervical veins were not distended. On auscultation of the lungs scattered rales were heard. The heart was enlarged to the right and to the left, with the left margin 2 fingers lateral from the mid-clavicular line. Gallop rhythm was heard. No hepatosplenomegaly, ascites or oedema were noted. The temperature was 38 °C, the pulse 40/min, the respiration 40/min and the blood pressure was 80 on palpitation.

Neurological examination revealed tetraparesis, the legs being more affected than the arms, diminished sensation to pinprick, temperature, and light touch in the lower legs and arms. Proprioception was intact, the knee and Achilles tendon reflexes were absent, biceps and triceps reflexes were diminished.

An electrocardiogram revealed sinus tachycardia and non-specific T-wave changes. Echocardiography showed enlarged right and left ventricles, with diminished wall movements and heart function. A roentgenogram of the chest taken minutes after admission showed a cardiothoracic ratio of 70% with pulmonary congestion and increased pulmonary vasculature (see Fig.6.1).

Examination of the blood disclosed no abnormal findings except for the blood thiamine level, which was 6.5 mμg/l (normal 11.3-47.8), and a high serum lactate level of 24 mEq/l (normal 0.5-2.2).

Haemodynamic studies are shown in Table 6.1.

Electrophysiological examination revealed an axonal polyneuropathy with abnormal H-reflexes, motor nerve conductions, and sensory nerve action potentials, especially in the distal extremities, and active denervation. Sural nerve and superficial sensory peroneal nerve somatosensory evoked potentials (SSEP) showed abnormally low amplitudes. The median nerve SSEP was normal. Stimulation and recording techniques were performed according to Delisa et al. (1987). Brainstem auditory evoked potentials (BAEP) were normal.

On the basis of the patient's history and clinical examination of alcoholism, nutrition, peripheral neuropathy, high cardiac output with biventricular failure, lactic acidosis and lack of other known causes of high output failure, the diagnosis of shoshin type beriberi heart disease was made. He was treated subsequently with TTFD (Thiamine Tetrahydrofurfuryl Disulfide) 2 x 25 mg intravenously, Bactrim forte (trimetroprim 80 mg + sulphamethoxazole 400 mg) 2 x 1 tablet, paracetamol 3 x 500 mg and sodium bicarbonate 7% infusion in accordance with the severity of the metabolic acidosis. The patient responded to the above management with a marked increase in urine output, correction of acidosis, improvement of skin colour and respiratory pattern. Chest X-rays taken 10 days later showed a return of the heart size to normal (see Fig. 6.1). One month after discharge the patient was still free of cardiac symptoms on a treatment with TTFD 3 x 50 mg a day. A mild peripheral polyneuropathy persisted. Electrophysiological findings showed marked improvements, with little augmentation of the amplitudes of the sural and superficial sensory peroneal nerves' SSEPs.

Case (2) A 50-year-old unemployed man was admitted to the Department of Cardiology, Dr. Soetomo Hospital, Surabaya, Indonesia, with dyspnea and a slight swelling of the legs and ankles. He lived on his wife's earnings as a servant (Rp 30,000 = US$ 18 00 a month). His diet consisted of large amounts of polished rice, hardly any meat, pulses or nuts. His wife cooked the rice herself, while the side dishes were delivered in dinner pails (Rp 400 = US $ 0.22 a day). He had also had some numbness and a tingling sensation in the lower extremities for 5 years Two months prior to admission, he began to notice excessive fatigue on exertion, oedema of the lower extremities, palpitation after walking, muscle cramps during the night and four-pillow orthopnea.

On examination, he appeared dyspneic, especially when lying down. The cervical veins were engorged and a few scattered rales were heard on examination of the lungs The heart was enlarged, the cardiac dullness extended 6 cm to the left of the mid-sternal line in the fifth intercostal space and 4 cm to the right of the mid-sternal line in the fourth intercostal space. The heart rate was 88/min with a regular rhythm; the temperature was 37.3 °C, respiration 40/min and blood pressure 115/70 mmHg. The liver and spleen were not palpable.

Examination of the nervous system revealed a marked decrease of muscle power in the lower legs. Particularly in the anterior tibial muscles there was marked atrophy and paresis. The deep reflexes of the lower extremities were diminished, whereas the biceps and triceps reflexes were normal. Plantar responses were normal. There was hypaesthesia to touch from the middle of the thigh downward. The sense of vibration was lost over the legs, and there was a diminution of the pain and temperature senses over the lower extremities Proprioception was intact.

Electrocardiography on day of admission demonstrated right bundle branch block (RBBB) and non-specific ST-T wave changes. The echocardiogram showed enlarged right atrial, right ventricular, left ventricular dimensions, with diminution of movements of the heart walls and heart function. The chest roentgenogram revealed cardiomegaly with biventricular enlargement, pulmonary vascular congestion and patchy infiltrates on the right and left paracardial regions, as well as thickened interlobar fissure margins (see Fig. 6.2).
Pertinent laboratory investigations showed no abnormalities except for the serum thiamine level, which was 5.7 mμg/l (normal 11.3-47.8).

Haemodynamic studies are depicted in Table 6.1.

Electrophysiological examination showed prolonged and low voltages of the H-reflexes, prolonged distal latency times of the peroneal nerves, and abnormal motor nerve conduction velocities of the distal extremities, consistent with axonal polyneuropathy. The amplitudes of the sural and superficial sensory peroneal nerves were very low. The median nerve SSEP was normal.

Based on the above mentioned data, the diagnosis of beriberi heart disease (chronic type) with beriberi polyneuropathy was made.

The patient was given digoxin, furosemide, TTFD 2 x 25 mg intravenously, and sodium bicarbonate 7%,in accordance with the level of acidosis. The digoxin and furosemide were gradually reduced and stopped, whereas the TTFD injection was exchanged for 3 x 50 mg TTFD tablets.

Seven days after admission, the patient had no dyspnea and no peripheral oedema. His lungs were clear, cardiomegaly had decreased (see Fig. 6.2).

Follow-up at home two months later showed that the patient had no cardiac symptoms. Evidence of mild peripheral neuropathy remained, though the dysaesthesia had improved. Electrophysiological findings showed some improvements.

Case (3) A 31-year-old motorized pedicab driver entered the Department of Cardiology, Dr.Soetomo Hospital, Surabaya, Indonesia, with complaints of two-pillow orthopnea which had started 7 days ago. His main diet consisted of large amounts of polished rice, fermented soybean cake, bean curd, and vegetables, but little or no meat, fish, pulses or nuts. During three years preceding admission, he had complaints of numbness and a tingling sensation in the extremities, especially when squatting or sitting on the floor with his legs crossed for a few minutes. For the past 7 days he had suffered from dyspnea when going upstairs.

On physical examination the patient was in respiratory distress and dyspneic when lying down. The weight was 43 kg, height 155 cm, and blood pressure 110/70 mmHg. The pulse was regular but high at 130 beats per minute, and weak. The patient had a respiratory rate of 42/min and a temperature of 37 °C. The cervical veins were distended to the angle of the jaw at 90 degrees deflection. Sounds of normal breathing as well as rales were heard over the bases of the lungs. The heart was enlarged to the right and to the left, with the left margin 2 fingers lateral from the mid-clavicular line and the right margin 4 cm from the mid-sternal line. Gallop rhythm was heard and a diastolic murmur on the apex. The liver was enlarged and could be palpated 3 fingers below the right costal margin, but the spleen was not palpable. No oedema or ascites were noted.

Neurological examination showed a slight weakness of the lower legs. Diminished sensitivity to pinprick and light touch in the lower legs. Proprioception was intact. The deep reflexes of the legs were absent, whereas the arm reflexes were diminished. No pathological reflexes could be elicited.

The electrocardiograms revealed sinus tachycardia at 140, incomplete right bundle branch block and non-specific ST-T wave changes. The echocardiogram demonstrated enlarged right ventricular, atrial, and left ventricular dimensions. The movements of the heart walls were diminished, no thrombus or pericardial effusion could be seen. X-rays of the chest showed a cardiothoracic ratio of 60% with increased pulmonary vasculature and no pleural effusion (see Fig. 6.3). Laboratory data showed normal values, except for the blood thiamine level which was 7.5 $\mu g/l$ (normal 11.3-47.8). Haemodynamic studies were done (see Table 6.1).

Electrophysiological examination revealed a slight axonal polyneuropathy, especially in the lower legs, with slight active denervation. The sural nerve SSEP showed low amplitudes. The superficial sensory peroneal nerve and median nerve SSEPs were normal.

Immediately after admission to the intensive care ward, therapy with nasal oxygen, furosemide, and 2 x 25 mg TTFD intravenously was started. Sodium bicarbonate 7% was also infused in accordance with the level of acidosis. This regimen appeared effective in reducing the severe dyspnea, with a marked increase in urine output. After 10 days in hospital, the electrocardiogram had returned to normal. X-ray of the chest showed a normal heart size (see Fig. 6.3). A diagnosis of cardiac beriberi of the chronic type with slight axonal polyneuropathy was made.

One month after discharge, when we visited the patient at home, he no longer had any cardiac symptoms There was still a mild peripheral neuropathy and the tendon reflexes of the lower extremities had not yet returned. He remained on 3 x 50 mg TTFD. Electrophysiological examination revealed great improvement.

6.3 DISCUSSION

The diagnosis of beriberi polyneuropathy in the above mentioned cases was based on the history of dietary inadequacy, electrophysiological signs of sensorimotor polyneuropathy, exclusion of other polyneuropathies (such as diabetes mellitus, uremia, leprosy, Guillain Barré syndrome, hereditary and toxic neuropathy) on the basis of clinical examination and biochemical findings. Most times it appears as a combined syndrome with polyneuropathy and cardiomyopathy.

SSEP examination may provide information often not yielded by the conventional neurophysiological examinations. SSEPs can sometimes be recorded even when nerve action potentials cannot be detected in the limbs, or when clinical examination fails to reveal a sensory deficit (Giblin, 1980). The most evident modifications are represented by longer latencies, clear amplitude decrease or considerable duration increase of different waves and of the evoked potential "in toto".

Thiamine is not stored in the body and the effects of its deficiency become apparent within a few weeks, particularly if the diet is high in carbohydrates (Carson, 1982).

The diagnosis of shoshin beriberi in case 1 is supported by the history of dyspnea, an inadequate diet consisting mainly of high amounts of polished rice in combination with a large non-fat caloric intake and excessive intake of alcohol. Furthermore, there were the symptoms of heart failure, signs of cardiogenic shock, lactic acidosis, peripheral neuropathy and a low level of blood thiamine. The heart enlargement seen in roentgenography was confirmed by echocardiography, which revealed enlargement of all chambers, increased cardiac output, and decreased heart function. Also the patient responded to thiamine and there were no signs of other cardiac disease.

The sudden cardiac failure is precipitated by strenuous exertion and fever with a resultant sudden increase in thiamine requirement. Besides, alcohol has a direct toxic effect on the myocardium.

In the West, the fulminant or pernicious variant of beriberi heart disease, termed shoshin beriberi, is rarely found (Attas et al., 1978).

The hands of case 1 were cold and cyanosed; this is in contrast with the emphasis placed by many on the warmth of the hands. The explanation is, that in early stages hand blood flow is increased because of vasodilatation in the muscle, but later, when heart failure appears, cutaneous blood vessels constrict to maintain the mean arterial pressure.

The severe metabolic acidosis in case 1 is explained by the elevated lactate level (metabolic acidosis). This can be explained as follows: thiamine deficiency combined with alcohol oxidation in the liver enhances the deficiency of nicotinamide-adenine-dinucleotide (NAD) and adds to the accumulation of pyruvate in blood and tissue. Besides, the deficiency leads to an inefficient functioning of the citric acid cycle (Majoor and Hillen, 1982). The high levels of pyruvate and NADH stimulate lactate production. Moreover, NADH enhances the β-OH-butyric acid-acidosis in alcoholics. McIntyre and Stanley (1971) said that in shoshin beriberi, peripheral oedema might be slight or even absent, as is seen in our case 1.

Cases 2 and 3 were examples of the Oriental non-alcoholic beriberi, caused by a staple diet of milled or polished rice, with hardly any meat, pulses or nuts. The reason for the high incidence of beriberi in the Orient is, that rice is washed three to six times, or until the rice washing is clear. Alejo et al. (1954) found a washing loss of 18.85% of thiamine in ordinary white unenriched rice, while an average of 35% of thiamine (ranging from 26.92 to 48.46%) is lost in cooking. Bhuvaneswaran and Screenivasan (1962) found a 55% loss of thiamine in washings and 30% in cooking.

In classic cardiac beriberi in the East, right heart failure occurs more often than left heart failure. In alcoholic cardiac beriberi as seen in the West, however, the pattern of the left heart failure with dyspnea, rales, and impaired left ventricular function is more common, so that the typical mode of presentation is biventricular failure with sinus rhythm (Carson, 1982). In contrast with our cases 2 and 3, biventricular failure is prominent. This is caused by advanced stages of thiamine deficiency, in which the cardiac beriberi relapses several times. Thus the cardiac dilatation may be only partially reversible or completely irreversible, according to degree and duration of myocardial involvement (Benchimol and Schlesinger, 1953). The diagnosis of beriberi heart disease in cases 2 and 3 is largely in accordance with Blankenhorn (1955).

Leukocyte transketolase activity may prove to be a more sensitive index of the thiamine deficiency than the erythrocyte transketolase activity (Braunwald, 1988).

Thiamine in small amounts of whole blood was determined by a simplified thiochrome method, which is less sensitive than erythrocyte transketolase activity and the determination of the TPP effect (Braunwald, 1988; Dreyfus, 1962).

Electrocardiographic changes in cardiac beriberi are not always non-specific. Weiss and Wilkinson (1937) mentioned auricular and premature beats in a small percentage of their cases. Frank T-wave inversion has been recorded in severe cases of thiamine deficiency. Complete left bundle branch block of the unusual type with right axis deviation was found in Benchimol and Schlesinger cases (1953), as in our cases 2 and 3. It is important to recognize, that some cases of beriberi heart disease do not show a complete normalization of the electrocardiogram after appropriate therapy, and that this should not necessarily rule out the diagnosis of thiamine deficiency.

Hypoproteinaemia has been reported as a common occurrence in beriberi. However, most of our patients seen during recent years had normal serum albumin and globulin concentrations. It is suggested that malnutrition is not an important factor in the pathogenesis of beriberi in Indonesia. Our cases all showed normal serum albumin and globulin.

Physical exertion, infectious disease, thyrotoxicosis, pregnancy, etc. play a tremendous role in the course of the disease. If the patient is not disabled by polyneuropathy and performs heavy muscular work, cardiac insufficiency results. If severe polyneuropathy is present, the myocardium is usually protected from the increased burden of muscular exercise (Keefer, 1930). The mechanisms of increased cardiac output and high output failure in cardiac beriberi are obscure. Some patients with beriberi have lesions of the sympathetic nuclei that may decrease peripheral arterial resistance and augmented venous return, thus increasing cardiac work and leading to congestive heart failure (Braunwald, 1988).

6.4 SUMMARY

In Indonesia subclinical cases of beriberi are not uncommon. Three patients suffering from beriberi presented with different clinical manifestations. One had the classical features of shoshin beriberi and the other two had the non-alcoholic cardiac beriberi (chronic type). The cardiac symptoms of all three patients responded dramatically to thiamine tetrahydrofurfuryl disulfide; there was also some improvement of their polyneuropathy, consistent with the neurophysiological findings and somatosensory evoked potentials (SSEPs) We conclude that SSEPs provide additional clinical information on beriberi polyneuropathy The mortality of untreated cardiovascular beriberi is high In view of the harmless nature of the treatment, a good case could be made for the routine administration of thiamine to all patients in whom heart failure is present without clear evidence of the cause.

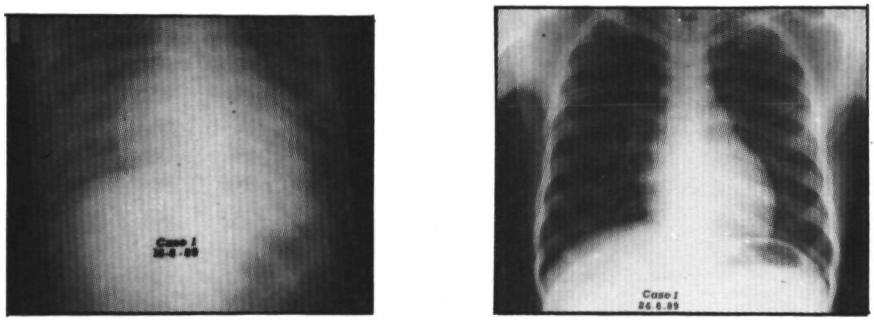


Figure 6.1 (Case 1). Chest roentgenogram: posteroanterior view. Left, generalized cardiomegali and pulmonary vascular congestion on day of admision. Right, disappearance of pulmonary vascular congestion and decrease in heart size ten days later.

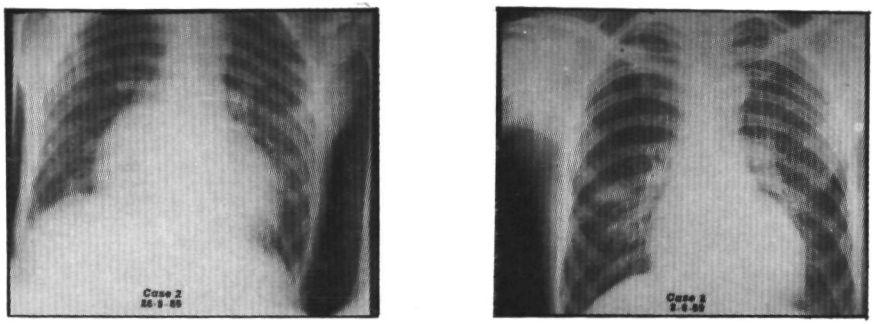


Figure 6.2 (Case 2). Chest roentgenogram taken on admission to hospital (left), and before discharge seven days later (right).

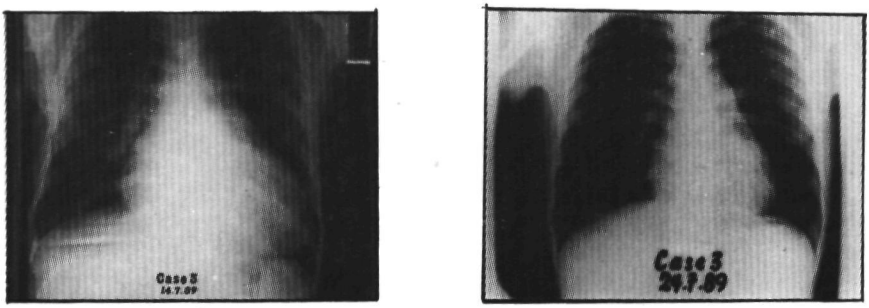


Figure 6.3 (Case 3). Chest X-rays at the time of admission (left), and after the patient's recovery ten days later (right).

TABLE 6.1 HAEMODYNAMICS BEFORE AND AFTER TREATMENT WITH TTFD

	CASE 1		CASE 2		CASE 3	
STUDY	INITIAL	AFTER	INITIAL	AFTER	INITIAL	AFTER
Weight (Kg)	50	47	61	52	45	40
Heart rate (beats/min)	140	88	130	88	140	80
Pressure (mm/Hg)						
Mean brach.art.	63	120	75	100	70	110
Mean R.atrium	20	10	26	12	20	8
R.ventricle, (end diastolic)	36	14	60	30	40	15
Mean pulm.art.	35	21	33	20	27	13
Aorta (mean)	67	109	65	120	75	130
Cardiac output (l/min)	23	8	20	8.3	17.2	7.8
Stroke volume/ ml/beat	123	105	125	100	120	104
Periph.vascular resistance (dyne-sec-cm-5)	325	1256	170	1356	160	1483
A-V O2 difference (volume %)	1.92	5.4	2.75	5.0	2.45	4.04
O2 consumption (ml/min STPD)	588	395	580	375	578	380
Minute ventilation (l/min STPD)	39.2	9.8	37.2	9.0	3.84	9.6
Respiratory rate/ min.	40	20	40	26	42	20

Note : Brach.art. = brachial artery
Periph. = peripheral
R. = right
Pulm.art. = pulmonary artery

CHAPTER 7

EXPERIMENTALLY INDUCED BERIBERI POLYNEUROPATHY IN CHICKENS

(Based on the article submitted to
Eur Arch Psychiatr Neurol Sci)

7.1 INTRODUCTION

The study of experimentally induced beriberi polyneuropathy in chickens was undertaken to verify the hypothesis that the nutritional polyneuropathy, as seen in our Department of Neurology in the Dr. Soetomo Hospital, Surabaya, was caused by thiamine deficiency. At the time this study started, verification through biochemical analysis was not possible, as the relevant testing materials were not available locally.

In 1890, Eijkman discovered by chance a chicken disease he designated "polyneuritis gallinarum", which closely resembled human beriberi. Therefore, the chicken appeared to be a suitable experimental animal for further studies into the pathogenesis of beriberi in humans. Chickens have the following advantages over other experimental animals, such as pigeons or rats: the clinical features in chickens are uniform and the course of the disease is slower than in pigeons, so that the chance they die during neurophysiological examination is very small. Neurophysiological examination in chickens is easier than in pigeons and rats, and the results are more reliable, since chickens are larger. Moreover, a special experimental laboratory is not required.

7.2 STUDY DESIGN AND METHODOLOGY

For this trial the same procedure was followed as in Eijkman's experiments (1896, 1927). The only difference was, that in our study the chickens were also given multivitamins (with the exception of thiamine), to prevent other vitamin deficiencies.

Material

Forty 16-week-old local chickens, purchased at the market by the author, were first given healthy food consisting of partially husked red rice with its bran, mixed with some unhusked rice and vegetables. Young chickens were chosen, because they react faster to vitamin deficiency than older ones and because they are of the same relative age group as our patients.

After 7-10 days on the above diet, the healthy chickens, kept in wire bottom cages, were divided into 2 groups:

Group I: twenty chickens, ranging in weight from 900 to 1250 g, mean 1086 ± 149.7 g (Table 7.2), received steamed milled white distributed rice ad libitum, 1 g/kg body weight protein [i.e. about 5 g tempe or 15 g bean curd or 1 g dried fish (stolephorus species)], a few drops of cod liver oil to prevent xerophthalmia, 50 g vegetables [e.g. Indonesian amaranth, swamp cabbage or "kangkung", mustard greens or "sawi"], 3 drops of multivitamins and a salt mixture. Each 0.3 ml (6 drops) of multivitamins consisted of riboflavin 500 mcg, pyridoxine 500 mcg, cyanocobalamin 1 5 mcg, niacinamide 5 mg and pantothenic acid 2.5 mg, which were supplied free of charge

by a pharmaceutical company. The contents of the salt mixture in grams per liter of solution were: NaCl (6.8), KCl (1.73), CaCl (0.64), NaHCO3 (2.45), MgSo4 (0.24) and pH 7.4. This salt mixture was ordered and purchased from a dispensary.
The rice was government-distributed rice, bought at the market. The composition of each nutrient per 100 g of the substance is shown in Table 7.1.

Group II: twenty control chickens with a mean weight of 926 ± 38.47 g (ranging from 890 to 990 g) were raised similarly on a complete ration, with the exception of the rice; in stead of steamed milled rice, they were given hand-pounded red rice still covered partly by its pericarp, which is sold at the market as bird feed. They were fed on this diet for 6 weeks, after which their diets were changed into the diets as in group I.

All the animals were fed twice daily and watered daily. When anorexia developed they were fed by force.

Examination

All the chickens were examined according to a special protocol (Annex 5). The examination consisted of: general examination, internal and neurological examination, neurophysiological examination, laboratory tests, and
neuromorphological examination.

General examination. General examination was performed by the author's wife and a resident of the Department of Neurology, Dr. Soetomo Hospital, Surabaya, in the author's garden.
During the general examination, observations were made regarding the animals' body weight, colour of face or comb, crowing, cackling, flapping wings, scratching, and appetite, as well as regarding colour of the stool, and their ability to walk along a horizontal roost Appetite was measured by the amount of food eaten or the diameter of the crop after eating. All the chickens were followed up weekly.

Internal and neurological examination. Internal and neurological examinations were carried out weekly by a resident of the Department of Neurology, Dr. Soetomo Hospital, Surabaya, and checked by the author. Attention was given to breathing, emptying of the crop, consciousness, sensory function, and motor function. All chickens were scored and followed up weekly. The scoring method allows a maximum of 10 points for a normal healthy chicken, divided as follows: normal breathing (1 point); normal emptying of the crop (1 point); normal sensation (1 point); normal consciousness (1 point); normal motor functions consist of normal standing (1 point); normal sitting (1 point), normal walking (1 point), normal running (1 point); normal position of head and neck (1 point); normal picking up of food (1 point).

Neurophysiological examination. Neurophysiological examination was done by the author with assistance of his wife, in the private practice of the author. Room temperature ranged from 32°-34°C. Electrophysiological studies included measurements of the motor conduction velocity of the peroneal and sciatic nerves, sensory nerve action potentials of the peroneal nerve, F-wave latency, as well as EMG of the gastrocnemius and peroneal muscles. Nerve conduction studies were done with the concentric recording needle in the first phalanx of digit III; stimulation with the cathode in the ankle or sciatic notch and the anode superior to it. Orthodromic sensory action potentials from the peroneal nerve were elicited by placing a recording

electrode (cathode) in the ankle and the anode 2 cm proximal to it. For stimulation of the peroneal nerve we used a concentric needle in the first phalanx of digit III. For the electroneuromyographic study a Medelec MS-92 was used. Long latency peroneal somatosensory evoked potentials (SSEPs) were also done. The active electrode was placed at CZ' (a few mm posterior to CZ), the reference electrode at FZ' (a few mm posterior to both eyes)(see Fig.1). Stimulation was done at the ankle, with the cathode placed 2 cm proximal to the anode. Equipment settings of the cortical SSEP were as follows: Analysis time 150 msec; gain - 15000; rate - 2.5; frequency bandwith - scalp recordings, 3 to 300 Hz; averager (sweeps averaged - 600 sweeps. For the SSEP study we used the Biologic Traveller U.S.A.

Laboratory tests. In the morning before breakfast, 1.5 ml blood was drawn by venipuncture of a wing's vein and placed into a tube containing 0.25 ml 2% oxalate mixture (3 parts ammonium oxalate and 2 parts potassium oxalate). The blood samples were taken as quickly as possible to the Department of Veterinary Medicine, Airlangga University, Surabaya, for haemoglobin and serum albumin examinations. Laboratory tests were done twice; once at the start of the study, and once after polyneuropathy had developed.

Neuromorphological study. Post-mortem nerve biopsies were conducted on the common peroneal and sciatic nerves shortly after death, whereas only the deep peroneal nerves were biopsied in chickens which were alive.
The biopsied nerves were fixed with 2% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.40) for 2 hours. The tissue was washed, postfixed in 1% osmium tetroxide for 2 hours, dehydrated and embedded into epoxy. Semi-thick epoxy sections (1 μm in thickness) were stained with toluidine blue and observed under a light microscope. The neuromorphological examinations were done by Gabreëls-Festen of the Department of Neurology, neuromorphological section, St.Radboud University Hospital, Nijmegen, The Netherlands.

Ex jubantibus treatment

After development of paresis, the animals in both groups were given 1 x 50 mg thiamine tetrahydrofurfuryl disulfide (TTFD) intramuscularly for 3 days, followed by 3 x 5 mg TTFD tablets for at least 3 months.

7.3 RESULTS

In group I, 29.6 ± 2.96 days after commencement of the diet the appetite of the animals decreased or disappeared completely, so that it was necessary to feed them forcibly. In spite of this, emptying of the crops was delayed, and they all lost weight (see Table 7.2).

Early signs of polyneuropathy were a paretic gait and now and then stumbling over their own feet. Abnormalities of posture and equilibrium, and difficulties in climbing their roost became evident. Soon thereafter, ataxia and uncontrolled backward movements occurred, indicating that both the gastrocnemius and peroneal muscles became paretic. The limbs were splayed and exhibited rapid, irregular, quivering motions. In severe cases, the toes became flexed and the animals could no longer stand; they sat on their tarsometatarsal and calcaneal bones. With advancing deficiency, the chickens could not sit upright anymore, and fell on their sides. A

rhythmic instability of head and trunk, or retracting and curling movements of head and neck were often observed.

Disturbances of respiration occurred only in some of the severe cases. Reduction of the respiration rate ranged from 18-20 per minute, seldom less than 10 per minute (normally 20-30/minute). The animals were apathetic and their eyes were closed by the nictitating membrane. The carotid pulses became rapid and shallow. Crest and gill became pale or cyanotic, and extremities were cold; there was dyspnea and cyanosis.

The onset of paresis, severe paralysis, and recovery of both groups are shown in Fig. 7.2 and Table 7.2. Sixty percent of the severe cases showed disturbed sensory functions. The stools became pulpous, greenish, in colour and frequent.

Haemoglobin and serum albumin contents did not change during and after the onset of paresis (Table 7.3).

Of the 40 animals, 6 died before institution of TTFD treatment. In one case convulsions developed just before death. The remaining 34 chickens responded dramatically to TTFD treatment (see Fig. 7.3).

The hearts of the 4 autopsied animals showed no remarkable abnormalities, weighing between 1-2 g (normal 1.5-2 g). In 2 cases the heart was enlarged (> 2 g). The lungs, spleen, and liver appeared normal. No serous fluids were found in the pericardial, pleural and abdominal cavities. The large intestines were distended and filled with gases, and the veins were engorged. The peripheral nerves appeared atrophic.

The neurophysiological abnormalities are shown in Tables 7.4 and 7.5.

Transverse epoxy sections of the deep peroneal nerves viewed under a light microscope showed some loss of large myelinated fibres. Mild myelin-folded changes were observed. The common peroneal and sciatic nerves showed only minor abnormalities (Fig. 7.5 a-b).

7.4 DISCUSSION

In this experiment, chickens were fed with the same composition of diet as our beriberi polyneuropathic patients. To prevent deficiencies of other vitamins of the B group, vegetables and multivitamin drops were administered. The general effects of inanition were controlled by giving adequate amounts of calories (± 40 cal./kg body weight) and the animals were force-fed when anorexia developed.

Our experiment demonstrated that chickens fed a diet of steamed milled white rice with all other vitamins of the B group except for thiamine, developed neuropathy resembling beriberi polyneuropathy in humans, whereas those given hand-pounded red rice remained healthy. This is in accordance with the classic experiments performed by Eijkman (1896, 1897, and 1927). The animals that stayed alive recovered after TTFD treatment. It is concluded that chickens fed with the same ration as our nutritional PNP patients developed beriberi PNP, and that partially husked red rice can prevent this disease.

In our experiment, all animals lost their appetite. This was caused by the monotony of the animals' diet. In spite of being force-fed, the animals' body weight gradually decreased, which indicates that thiamine has an effect on the resorption and metabolism of the nutrients. Stasis of the large intestines and engorgement of the veins were encountered in our experimental animals. Although thiamine deficiency was accompanied by loss of body weight, the inanition was not the cause, since starvation experiments on chickens did not cause nerve degeneration (Eijkman, 1913).

The peroneal nerves were the most affected. This is in accordance with beriberi polyneuropathy in man, in which the large, long and superficial nerve fibres were the first to degenerate.

The chickens in group II developed paresis later than those in group I. It seemed that they could store more thiamine in their bodies during the pre-study period, which was then utilized during the period of deficient thiamine intake.

In 1 of the 40 chickens (2.5%) convulsions developed prior to death. Convulsions have been reported in experimentally induced thiamine deficiency in pigeons and beagles (Itokawa, 1975; Read and Harrington, 1981). In a retrospective study, de Bruyn and Keyser (unpublished data, 1988) found 32% disturbances of consciousness and 18% convulsions in thiamine deficient patients who were admitted to the Department of Neurology, St Radboud Hospital, Nijmegen, in the period 1968 to 1983. The relationship between thiamine deficiency and convulsions is still obscure. A deficiency of the gamma aminobutyric acid (GABA), a disturbance in the cytochrome oxidase with a decrease of the ATP production, a reduction of the Krebs cycle with a shift to the GABA succinate shunt with disturbance of the local regulation of the potassium, sodium, calcium and magnesium, are among the hypothetical causes of epileptic fits in thiamine deficiency (Itokawa, 1975; Schoffeniels et al., 1984).

In this study, electromyographic findings, characterized by fibrillation potentials and positive sharp waves (100%) with minimal changes of the maximum motor conduction velocities of the peroneal nerves (20%), were compatible with a major degree of axonal degeneration and minimal segmental demyelination.

SSEP testing is particularly useful because the clinical sensory neurological examination is often difficult and unreliable, especially in infants, young children, and animals (Levy, 1990). Axonal loss produces amplitude changes without latency shifts, since the remaining axons will be conducting at normal velocities. A mixture of segmental demyelination and axonal loss results in a combination of latency delays and amplitude changes in SSEP recordings (Chiappa, 1990). In alcoholic neuropathy, Bergamini et al. (1965) found latency and duration increases in all cases during SSEP testing. Fifty percent of our experimentally induced beriberi neuropathy showed a combination of latency delays and amplitude changes. In 2 of the cases, SSEPs were unrecordable (see Fig.4b). It seems likely that this was due to extensive degeneration of the distal ends of fibres in the posterior column (Le Quesne, 1983, Gabreëls-Festen, 1988).

Shaw and Philips (1945) provided further evidence that chronic thiamine deficiency results in degeneration of the peripheral nerves in pigeons and they observed similar changes in chicks. More recently, Prineas (1970) described the ultrastructural changes in the peripheral nerves of thiamine-deficient rats. The changes took the form of an accumulation of flattened membrane-bound sacs and a concurrent depletion of neurotubules and neurofilaments in the axoplasm of the most distal branches of the lower motor neuron and the centripetal extensions of the first sensory neurons within the central nervous system.

In our case the deep peroneal nerves of the animals showed some loss of large myelinated fibres and mild myelin-folding changes (see Fig. 7.5b) The sciatic nerves showed only minor abnormalities.

Ultrastructural and teased-fibre studies of the sural nerves in humans with beriberi neuropathy showed that axonal degeneration was the most prominent feature, and that large myelinated fibres were more affected than unmyelinated ones. Accumulation of flattened sacs or tubuli was recognized in axoplasm of myelinated fibres. The

ratio of axonal degeneration and segmental demyelination was 37.5% to 5.3% (Takahashi and Nakamara, 1976, Ohnishi et al., 1980; Wadia, 1984).

7.5 SUMMARY

Chickens fed with the same composition of diet as our low income beriberi polyneuropathic patients developed clinical symptoms of thiamine deficiency which recovered after TTFD treatment. The development of neuropathy is proved by the neurophysiological and neuromorphological findings, i e. a major degree of axonal degeneration and secondary minimal segmental degeneration.
There appeared to be a body store of thiamine which is utilized during a period of deficient intake.
Haemoglobin content and serum albumin did not change appreciably during thiamine deficiency.

TABLE 7.1 COMPOSITION OF THE NUTRIENTS PER 100 G OF THE SUBSTANCE

Substance	Cal.	Prot. g	Fat g	Cbh g	Ca mg	P mg	Fe mg	A I.U.	B1 mg	C mg
Milled white rice	360	6.8	0.7	78.9	6	140	0.8	-	0.12	-
Red rice	359	7.5	0.9	77.6	16	163	0.3	-	0.24	-
Rice bran	275	12.6	14.8	54.6	32	2000	14.0	-	0.82	-
Cod liver oil	902	-	100.0	-	-	-	-	80000	-	-
Tempe	149	18.3	4.0	12.7	129	154	10.0	-	0.17	0
Bean curd	68	7.8	4.6	1.6	124	63	0.8	-	0.06	0
Dried fish*	170	33.4	3.0	-	1200	-	3.6	-	-	-
Swamp cabbage	29	3.0	0.3	5.4	73	50	2.5	6300	0.07	32
Indonesian amaranth	36	3.5	0.5	6.5	267	67	3.9	6090	0.08	80
Mustard greens	22	2.3	0.3	4.0	220	38	2.9	6460	0.09	102

* stolephorus species = a kind of small fish
swamp cabbage = Ipomoea reptans (kangkung)
mustard greens = Brassica Juncea (sawi)
Cal. = calories Prot. = protein Cbh = carbohydrate
Ca = calcium P = phosphor Fe = iron
A = vitamin A B1 = vitamin B1 C = vitamin C
g = gram

TABLE 7.2 EXPERIMENTALLY INDUCED BERIBERI NEUROPATHY IN CHICKENS

	GROUP I	GROUP II
BODY WEIGHT (G)		
Start	1086 ± 149.2	926 ± 38.47
Paresis	1076 ± 148.1	1300 ± 91.37
Paralysis	1028 ± 130.3	1100 ± 102.29
ONSET (DAYS)		
Paresis	22.3 ± 6.3 (15-33)	63.6 ± 24.3 (41-104)
Paralysis	31.0 ± 6.2 (17-40)	90.8 ± 22.4 (65-118)
Recovery from paralysis	35.7 ± 8.1	32.2 ± 6.5
SCORE		
Paresis	9.30 ± 0.35	9.2 ± 0.42
Paralysis	4.95 ± 1.57	4.7 ± 2.04
Recovery	10	10

TABLE 7.3 BIOCHEMICAL FINDINGS

	START	AFTER P.N.	NORMAL VALUE
Hb (g%)	13.05 ± 1.57	13.22 ± 1.5	10.11 ± 0.53 14.62 ± 1.33 (Ross et al., 1978)
S.albumin (g%)	2.06 ± 0.15	2.02 ± 0.11	1.53 ± 0.30 2.02 ± 0.08 (Ross et al., 1978)

Hb = haemoglobin S = serum
P.N.= polyneuropathy

TABLE 7.4 MOTOR / SENSORY NERVES

NERVE	ABNORMAL (%)	NORMAL VALUE
PERONEAL MOTOR		
Latency time		
ankle	60	2.2 ± 0.3 msec
knee	40	4.42 ± 0.56 msec
Amplitude		
ankle	60	1500 ± 428.4 μV
knee	60	1530 ± 548.33 μV
MCV	20	45.3 ± 5.2 m/sec
SCIATIC MOTOR		
Latency time		
sciatic notch	20	5.46 ± 0.6 msec
Amplitude		
sciatic notch	60	1505 ± 432.08 μV
MCV	40	63.71 ± 14.2 m/sec
PERONEAL SENSORY		
Distal latency	60	1.35 ± 0.19 msec
Distal amplitude	0	6.5 ± 3.34 μV

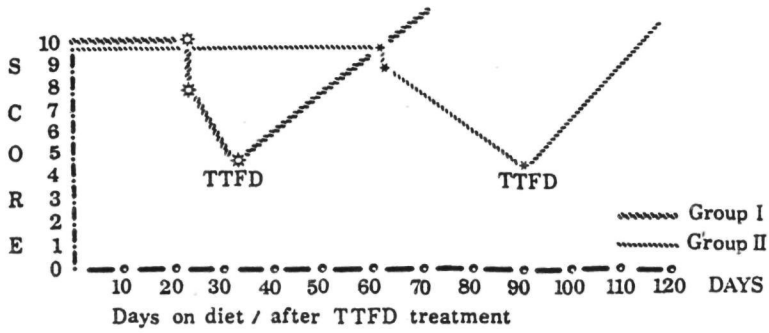
MCV = motor nerve conduction velocity

TABLE 7.5 F-WAVE LATENCY / CORTICAL SSEP / MUSCLE

SITE	ABNORMALITY (%)	NORMAL VALUE
F-WAVE		
ankle	100	13.06 ± 1.56 msec
knee	100	12.22 ± 1.53 msec
AMPLITUDE F-WAVE		
ankle	0	295 ± 260.8 μV
knee	0	380 ± 407.7 μV
DEEP PERONEAL NERVE SSEP (long latency)		
P1	50	18.93 ± 1.8 msec
N1	50	28.38 ± 1.8 msec
GASTROCNEMIUS AND PERONEAL MUSCLES	100	-

SSEP = somatosensory evoked potential

Fig.7.1 Placement of the electrodes in somatosensory evoked cortical potential registration.



EXPERIMENTALLY INDUCED BERIBERI PNP IN CHICKENS

Fig. 7.2 The development of thiamine deficiency in chickens in group I and group II. TTFD treatment resulted in recovery of the thiamine-deficient animals.

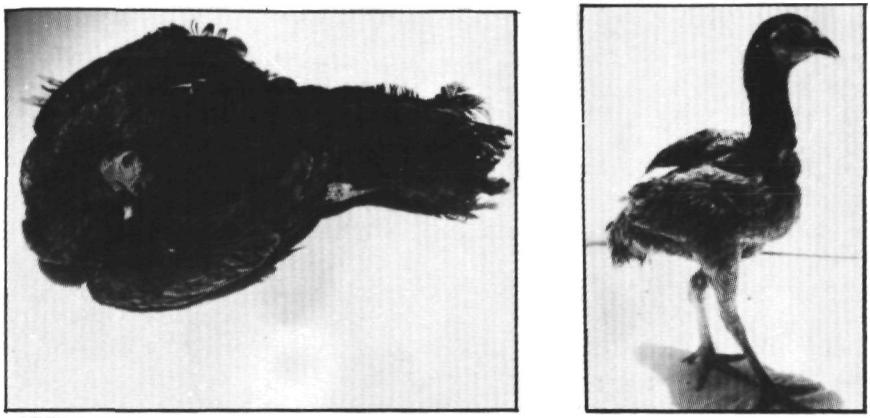


Fig. 7.3 a, b Left: a chicken with thiamine deficiency neuropathy. Right: the same chicken, recovered after TTFD treatment.

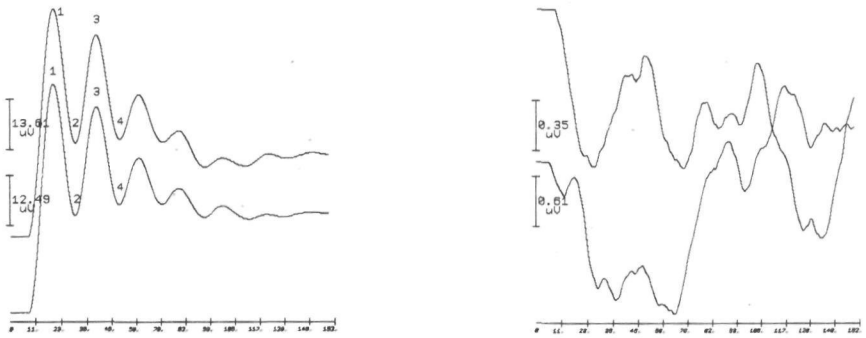


Fig. 7.4 a,b Normal and unrecordable somatosensory evoked cortical potentials in a normal and a thiamine-deficient neuropathic chicken.

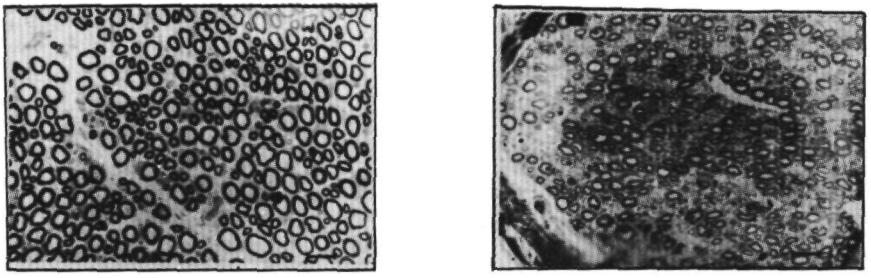


Fig. 7.5 a,b Transverse section of the deep peroneal nerve in control chicken (left) and in a chicken with experimentally induced thiamine deficiency (right). Note the decrease in density of the large myelinated fibres. (Toluidine blue staining, x 142, epon coupe 1 μm, bar = 18 mm).

CHAPTER 8

SUBCLINICAL BERIBERI POLYNEUROPATHY

(Based on the article submitted to
Journal of Tropical and Geographical Neurology)

8.1 INTRODUCTION

Beriberi polyneuropathy was found to be quite prevalent in patients from lower income groups, admitted to the Department of Neurology, Dr. Soetomo Hospital, Surabaya. It is important to know, whether these clinical cases are just the tip of the iceberg, while marginal, subclinical beriberi PNP may be far more common. To assess its prevalence rate a group of non-PNP persons were examined.

8.2 STUDY DESIGN AND METHODOLOGY

A. Subjects

The subjects were healthy individuals from the low, middle, and high income groups.

The low income group series (group I) consisted of persons with a monthly budget of less than US$ 20.-. They were friends or relatives of non-PNP patients presenting to the neurological outpatient clinic of the Dr.Soetomo Hospital, Surabaya, in 1989. The middle and high income groups (group II) were randomly chosen from students of the Medical School, Airlangga University, or the Institute of Technology, both in Surabaya, and people visiting the neurological inpatient clinic of the Dr.Soetomo Hospital, Surabaya, in 1989. All these subjects lived on a budget exceeding US$ 20.- a month.

We explained the purpose of the study and asked preliminary information from those eligible and willing to participate.

The diagnosis of subclinical beriberi polyneuropathy was based on obscure clinico-neurological and electrophysiological signs of sensorimotor polyneuropathy, exclusion of other polyneuropathies, for instance Guillain Barré syndrome, or PNP caused by diabetes mellitus, uremia, leprosy, or intoxication; and low blood thiamine levels according to Myint and Houser (1965).

B. Examination

Internal, psychiatric, and neurological examinations, as well as laboratory studies were performed according to special protocol sheets (Annex 3). Neurophysiological evaluation was done according to Annex 4.

For information on diets we used a special food pattern survey sheet (Annex 6) This was done by a nutritionist of the Department of Nutrition, Dr. Soetomo Hospital, Surabaya.

We used the 24-hour recall method and a food frequency questionnaire. The nutritients of each food were calculated on the basis of food composition tables. We calculated only the amount of calories, protein, fat, carbohydrate and thiamine contained in the subjects' diets.

We measured their heights and weights and calculated their body mass index (BMI). The BMI or Quetelet's index has been proposed for determining ideal body weight for height: [BMI = W/H^2 (W is weight in kilograms; H is height in meters)]. A BMI greater than 27 for either sex is indicative of obesity (Krause and Mahan, 1984), whereas a BMI less than 19 denotes slimness (Bray, 1983).

Internal, psychiatric and neurological examinations were done by an assistant neurologist of the Department of Neurology, Dr.Soetomo Hospital, Surabaya, and checked by the author. The subjects were referred to the Departments of Internal Medicine or Psychiatry of the Dr. Soetomo Hospital, if this was considered necessary.

Neurophysiological examinations were performed by the author with the assistance of his wife, as described previously.

Laboratory studies, such as electrocardiogram and X-ray of the chest were routinely done, as well as blood examinations (Table 8.12). The subjects were instructed to stop taking any medication, including multivitamins, three days (wash-out period) before blood thiamine examination.

8.3 RESULTS

There were 53 persons in the low income group (group I), 26 males and 27 females. The middle and high income groups (group II) consisted of 56 subjects, 28 males and 28 females. In group I, 35 patients (66%) appeared to have subclinical PNP, in group II, 7 patients (12.5%). The prevalence rate of both groups was 38.5% (Table 8.1). Most of them were between 15 and 30 years old (Table 8.2). The mean age of the male and female patients (group I and II) was 21.1 $\pm$ 3.3 years and 20.7 $\pm$ 3.2 years, respectively The male to female ratio was 1 6·1 (Table 8 2) They were mostly (66.7%) pupils of the secondary school and students (Table 8.3). 61.9% had a BMI of less than 19 and only a few (9.5%) were obese (Table 8.4). Confounding factors were present in a small percentage of the cases, such as alcoholism (9.5%) and chronic hepatitis (7.1%) (Table 8.5).

Diet. Analysis of the diets of the subclinical PNP patients showed that 78.2% of the 2069.2 calories they ingested daily were from carbohydrates, whereas 11.2% and 10.6% were from fat and protein, respectively. The thiamine intake was 0.24 $\pm$ 0.09 mg/1000 kcal (Table 8.6).

In the non-PNP subjects, the amount of calories ingested was 2670.1 $\pm$ 858.4, of which 66.5%, 23.1% and 10.3% were from carbohydrates, fat, and protein, respectively. Their thiamine intake was normal (0.47 $\pm$ 0.01 mg/1000 kcal) (Table 8 6).

In the subclinical PNP patients, government-distributed milled rice was the staple food. Complementary foods such as cassave, yam, potatoes, white bread, and corn were consumed irregularly. Thiamine-rich foods, such as duck eggs, mung beans, cow peas and soy milk, were consumed rarely. "Tempe" (fermented soybeans) and "tahu" (soybean curd) were regularly eaten. Fish, meat (cow and chicken), and chicken eggs were less frequently consumed.

Vegetables formed part of the daily menu. Leafy vegetables were less often consumed (Table 8.7).

Internal, psychiatric and neurological examinations. On internal examination it was found, that 3 patients suffered from chronic hepatitis. No psychiatric abnormalities were encountered.

Neurological examination showed the following findings. The common complaints of subclinical beriberi polyneuropathy in both groups were numbness or a tingling sensation in the distal portions of the extremities (40.5%), easy fatigability (35 7%), muscle cramps (26.2%), cold extremities (19%) and profuse sweating (11.9%). All these symptoms were usually insidious in onset (months to years). Irritability and oedema of the feet were seldom encountered (see Table 8.8).

The only demonstrable signs of neuropathy during physical examination were a slight paresis of dorsiflexion of the great toe (57.1%), slight disturbances of the senses of touch (40.5%), pain and temperature (38.1%), especially in the distal portions of the legs, and depression of the ankle (40.5%) and knee jerk reflexes (30.9%). The signs of neuropathy in the arms were usually less pronounced than in the legs. Vibration and position senses were affected in only 7.1 and 2.4% of the cases, respectively. 11.9% showed tenderness of the calf muscles. True distal and symmetrical glove-stocking sensory disturbances were only found in a small percentage of cases (not cited in the table). Burning feet or painful extremities were not found. Brisk ankle and knee jerks were found only in one case (2.4%) (Table 8.9).

Neurophysiological examination. The neurophysiological abnormalities in both groups are depicted in Tables 8.10 and 8.11.
Out of all the neurophysiological parameters assessed, reduced amplitudes of the distal latency of the peroneal motor nerve (64.3%) and H-reflex (57.1%), and pathologic EMG findings in the leg muscles (57.1%) were the most frequently occurring abnormalities, followed by reduction of the proximal amplitude of the peroneal motor (52.4%) and distal amplitude of the sural sensory nerve (26.2%). However, the motor conduction velocities of the peroneal, posterior tibial and median motor nerves were all within normal limits. The distal amplitudes of the motor (peroneal and median) and sensory (sural and median) nerves were more affected than the distal latency times.

Laboratory studies. Electrocardiograms and chest X-rays were within normal limits. Three patients showed abnormal serum glutamic-oxaloacetic and glutamic-pyruvic transaminases, respectively. All other laboratory tests were normal, except for the low blood thiamine levels in all the subclinical PNP patients, i.e. 9.0 ± 1.8 mμg/ml (normal 11.3 - 47.8 mμg/ml) (Table 8.12).

8.4 DISCUSSION

From this study it became clear, that the prevalence rate of subclinical beriberi PNP in our apparently healthy subjects was 38.5%. The exposure odds ratio for group I versus group II was 13.6, indicating that the low income group ran a greater risk of developing beriberi PNP than the middle and high income groups.
Higher income groups can afford better quality food of a greater variety; the diets of the subjects in group II were usually varied and wholesome (Table 8.7).
To our knowledge, so far in Indonesia no community-based studies of beriberi PNP have been reported. Chen et al. (1984) found a 34% incidence of beriberi in peasants, who discarded the water in which the rice was cooked (instead of using it for further consumption). Wadia (1984) reported 41.8% thiamine deficiency neuropathy in malnourished patients.

It seems that the low amount of ingested thiamine (0.24 ± 0.09 mg/1000 kcal), which is reflected in the low blood thiamine levels (9.0 ± 1.8 mμg/ml), was the main cause of the thiamine deficiency in our subclinical PNP patients.
The minimal thiamine requirement of the adult human is 0 40 mg/1000 kcal (WHO, 1976). Chen et al. (1984) observed that beriberi did not occur when thiamine intake was higher than 0.34 mg/1000 kcal.
Thiamine-rich food, such as duck eggs, cow peas, mung beans, and soy milk were never consumed by 83.3%, 58.3%, 33.3%, and 100%, respectively, of the subclinical PNP patients (Table 8.7). Sri Kardjati et al. (1979) reported that in the regency of Sidoarjo, 20 kilometres from Surabaya, the median daily intake of thiamine was low, ranging from 38-75% of RDI (recommended daily intake) among non-pregnant, non-lactating mothers.
The mean energy intake of our subclinical PNP patients was 2069.2 ± 121.88 kcal, the mean protein, fat and carbohydrate intake was 55.11 ± 4.88 g (10.6% of total kcal); 25.66 ± 11.97 g (11.2% of total kcal) and 404.4 ± 31.63 g (78.2% of total kcal), respectively.
The quantity of protein consumed as a percentage of energy intake was on average just sufficient. This is in accordance with the nutritional survey of Sri Kardjati et al. (1979) and Kusin (1986).
The amount of fat consumed seemed to be very low, i.e. 11.2% of the calories ingested. Sri Kardjati et al. (1979) found that the range in median intake of fat for the above category of mothers was very low in all areas of Sidoarjo and Madura, i e. 13-25 g per day; for non-breast fed children it was 6-18 g per day.
Carbohydrates constituted 78.2% of the energy intake of our patients, mainly in the form of steamed milled rice In Sidoarjo, rice was the main source of energy for the above mothers (71-82%), followed by fats (8-11%), and pulses (4-8%). In Madura, an even higher percentage of the daily energy intake was supplied by the staple food (86-90%), a small percentage was derived from fish (3-6%) and fats (3-4%) (Sri Kardjati et al., 1979).
Since thiamine requirement mainly depends on non-fat calories in the diet, ingestion of carbohydrate-rich diets deficient in thiamine may provoke thiamine deficiency.

The most salient facts noted in our patients were the monotony of their diets and the irregularity of consumption of foodstuffs other than the staple foods (Table 8.7). The habitual diet consisted of rice, "tempe" (fermented soybeans), "tahu" (soybean curd) and non-leafy vegetables.

In subclinical beriberi PNP, men were more affected than women, especially in the younger age group (15-30 years). This is in accordance with the findings of Mengistu and Maru (1979) and Chen et al. (1984) in their beriberi patients.

Tingling sensations in the distal parts of the extremities, easy fatigability, and muscle cramps in the lower extremities were the most prevalent symptoms of subclinical beriberi PNP. The symptoms had started months or even years earlier, indicating a chronic thiamine deficiency.
Slight paresis of dorsiflexion of the feet or great toes, disturbances of touch, pain, and temperature senses, as well as decreased ankle jerks were the most frequently observed abnormal neurological signs. Decreased ankle jerks seemed to be the most reliable objective sign, especially in less cooperative patients.
Tenderness of the calf muscles on pressure was found in 11.9% of the cases, whereas brisk ankle and knee jerks were rarely encountered (2.8%).
Chen et al. (1984) reported that the early symptoms of beriberi were heaviness and weakness of the legs, tenderness of the calf muscles on pressure, and "pins and needles" and numbness in the leg. The tendon jerks were usually sluggish and

anaesthesia of the skin, especially over the tibia, was common Demeke and Habte-Gabr (1982) found difficulty in walking (88%), calf and thigh pains (72%), knee joint pain (24%), numbness of leg and foot (20%), stiffness of lower limbs (8%), swelling of leg (52.5%), knee (12%), and thigh, foot, and hand (4%) in 25 patients suspected of dry beriberi.

The following symptoms and signs were encountered by Mengistu and Maru (1979) in 13 cases of dry beriberi: heaviness and numbness of legs (92.3%); swelling of legs (92.3%); burning pain in legs (76.9%); inability to walk (100%); inability to rise from a squatting position (100%); tenderness in the legs (100%); impaired vibration and position senses (100%); brisk ankle and knee jerks (92.3%) and reduced heat, pain, and touch sensations (69.2%). The duration of the illness ranged from 2 to 20 weeks.

The centripetal axonal degeneration (dying back) as in thiamine deficiency appears to involve initially the most terminal and peripheral segments of the longest fibres, which are the most vulnerable. The primary lesion in beriberi polyneuropathy is axonal degeneration, while changes in the myelin are secondary (Kimura, 1984)

Mild axonal polyneuropathy may be present without abnormalities of nerve conduction velocity, especially if the disease primarily affects the small fibres (Kimura, 1984). The motor conduction velocities of the peroneal, posterior tibial, and median nerves of our cases were all within normal limits, except for low amplitudes of the distal and proximal latencies of the peroneal nerve (64.3% and 52.4%, respectively) (see Table 8.10).

A prolonged latency also occurs in axonal neuropathy if the fastest conducting fibres are lost. In this case, the amplitude would be significantly reduced as well (Kimura, 1984). In 19% of our cases, the distal latency of the peroneal motor nerve was reduced, but less severely than the distal amplitudes (64.3%) (see Table 8.10)

In diabetes and alcoholism, H-reflex measurement rivals the conventional nerve conduction studies in early detection of neuropathic abnormalities (Notermans, 1984, Kimura, 1984; Kimura, 1983; Lefebvre et al., 1979, Murai and Kuroiwa, 1973) 57.1% of our subclinical beriberi polyneuropathies showed an abnormality of their H-reflex over the soleus muscles (see Table 8.11).

In axonal polyneuropathy, the compound muscle action potential is also reduced in amplitude, reflecting loss of nerve fibres (Kimura, 1984). Reduced amplitudes of the compound muscle action potential were found in 26.2% of our cases (see Table 8.11)

Positive sharp waves tend to appear before the fibrillation potentials following nerve section. It has been postulated that positive sharp waves represent single fibre discharges recorded from an injured area of the fibre (Kimura, 1984, Wiechers, 1977)

In our study, denervation activity consisting of positive sharp waves was recorded over the anterior tibial muscles in 57.1% of the cases, whereas in only 2.4% it consisted of fibrillation potentials (see Table 8.11). EMG studies are more sensitive to neuropathic changes than conduction velocities (Lamontage and Buchtal, 1970, Mulder et al., 1961) and are able to detect denervation abnormalities before the fastest motor velocities become slowed (Hansen and Ballantyne, 1977).

Reduction of sensory potential amplitudes (Noël, 1973, Lamontage and Buchtal, 1970) is an early electrophysiological sign of diabetic polyneuropathy In general, sensory potential amplitudes in the foot decrease before amplitudes are reduced in the hand. Lefebvre et al (1979) found that 84% of their patients with alcoholic neuropathy had abnormalities of the sural nerve conduction, but only 73% showed an abnormality of median and ulnar nerve sensory conduction

Of our patients, 26.2% showed abnormalities of the distal amplitudes of the sural sensory nerve conduction, but only 7.1% in the median sensory nerve conduction (see Table 8.11).

8.5 SUMMARY

Of the apparently healthy subjects in our study, 38.5% appeared to have subclinical beriberi polyneuropathy Subjects in the low income group had a greater risk of developing beriberi PNP than those from the middle and high income groups. Assessment of nutritional status concerning thiamine by blood levels and analyses of the subjects' diets revealed low blood thiamine levels and a low thiamine intake.

Tingling sensations in the distal portion of the exremities, easy fatigability with slightly paretic dorsiflexion of the feet or great toes, slight disturbances of touch, pain, and temperature senses, especially in the distal portions of the legs, and depression of the ankle jerks were the most prevalent neurological symptoms and signs of subclinical beriberi polyneuropathy.

Out of all the neurophysiological evaluations assessed, reduced distal amplitudes of peroneal nerve and H-reflex, as well as denervation activity in electromyography were the most frequently found abnormalities, followed by reduced amplitude of the proximal latency of the peroneal motor nerve and, much less frequently, of the sural nerve action potentials.

TABLE 8.1 SUBCLINICAL BERIBERI POLYNEUROPATHY

GROUP	NO.OF PNP PRESENT	PATIENTS ABSENT	RATE (PERCENT)	OR
LOW INCOME (I)	35	18	66	13.6
MIDDLE & HIGH (II) INCOME	7	49	12.5	
TOTAL	42	67	38.5	

PNP = polyneuropathy ; OR = exposure odds ratio

TABLE 8.2 AGE AND SEX DISTRIBUTION (SUBCLINICAL PNP)

AGE RANGE (YEARS)	LOW INCOME (35 patients) MALE	FEMALE	MIDDLE & HIGH INCOME (7 patients) MALE	FEMALE	TOTAL (42 patients) MALE	FEMALE
< 15	-	-	-	-	-	-
15 - 30	17	10	4	2	21	12
31 - 50	3	1	-	1	3	2
51 OR OLDER	2	2	-	-	2	2
TOTAL	22	13	4	3	26	16
MEAN AGE	21.3	20.6	20.2	20.7	21.1	20.7
SD	3.5	3.4	1.5	3.2	3.3	3.2

SD = standard deviation

TABLE 8.3 OCCUPATION (SUBCLINICAL PNP)

OCCUPATION	LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	TOTAL (%) (42 patients)
PUPILS	10		10) (66.7)
STUDENTS	14	4	18)
EMPLOYED	7	3	10 (23.8)
UNEMPLOYED	4	-	4 (9.5)
TOTAL	35	7	42

TABLE 8.4 BODY MASS INDEX (BMI)
(SUBCLINICAL PNP)

BMI	LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	TOTAL (%) (42 patients)
> 27	1	3	4 (9.5)
> 19 < 27	12	-	12 (28.6)
< 19	22	4	26 (61.9)
TOTAL	35	7	42

TABLE 8.5 CONFOUNDING FACTORS
(SUBCLINICAL PNP)

CONFOUNDING FACTOR	NUMBER OF PATIENTS LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	TOTAL (%) (42 patients)
ALCOHOLISM	3	1	4 (9.5)
CHRONIC HEPATITIS	2	1	3 (7.1)
ALLERGY	1	-	1 (2.4)
PREGNANCY	1	-	1 (2.4)
PUERPERIUM	1	-	1 (2.4)
SPRINTER	1	-	1 (2.4)
TOTAL	9	2	

TABLE 8.6 ANALYSIS OF THE DIETS
(SUBCLINICAL PNP VS NON-PNP)

ITEM	SUBCLINICAL PNP (42 patients)	NON-PNP (67 patients)	NORMAL VALUES
KCAL	2069.02 ± 121.88	2670 ± 858.4	35-40 kcal/kg/day (light activity) (Krause and Mahan, 1984)
PROTEIN (G)	55.11 ± 4.88	69.3 ± 18.2	0.8 g/kg (10-20% of total kcal) (Krause and Mahan, 1984)
FAT (G)	25.66 ± 11.9	69.0 ± 14.2	1-2 g/kg (25-35% of total kcal) (Krause and Mahan, 1984)
CARBOHYDRATE (G)	404.4 ± 31.63	445.9 ± 192.1	4-6 g/kg (50% of total kcal) (Krause and Mahan, 1984)
B1 INTAKE	0.24 ± 0.09	0.47 ± 0.01	0.4 mg/1000 kcal (FAO/WHO, 1967)
HEIGHT	161.2 ± 9.8	162.6 ± 8.98	
WEIGHT	47.8 ± 9.96	53 ± 9.7	

vs = versus

TABLE 8.7 FOOD FREQUENCY QUESTIONNAIRE (SUBCLINICAL PNP VS NON-PNP)

SUBSTANCE	1-3X/DAY		3-6X/WEEK		SELDOM 1-2X/WEEK OR MORE		NEVER	
GROUP (% CONSUMED)	+	-	+	-	+	-	+	-
> 0.5 MG VITAMIN B1/100 G SUBSTANCE								
DUCK EGG YOLK	0	0	0	42.8	16.6	14.3	83.3	42.8
MUNG BEANS	0	0	0	14.3	66.7	71.4	33.3	14.3
COW PEAS	0	0	0	14.3	41.7	57.1	58.3	14.3
SOY MILK POWDER	0	0	0	0	0	28.6	100	71.4
0.1 MG - 0.5 MG VITAMIN B1/100 G SUBSTANCE								
LEAN COW'S MEAT	0	28.6	50	28.6	33.3	42.8	16.6	0
CHICKEN EGG	8.3	57.1	50	14.3	25	28.6	16.6	0
DECAPTERUS KURRA (PINDANG)(A KIND OF FISH)	0	0	16.6	28.6	50	28.6	41.7	- 42.8
STOLEPHORUS SPECIES (TERI)(A KIND OF FISH)	0	0	0	0	25	28.6	75	71.4
MILK	0	14.3	16.6	28.6	41.7	14.3	41.7	42.8
FERMENTED SOYBEANS (TEMPE)	33.3	71.4	58.3	14.3	8.3	14.3	0	0
PEANUTS	8.3	14.3	50	42.8	41.7	42.8	0	0
MILLED RICE	100.0	100.0	0	0	0	0	0	0
GLUTINOUS RICE	0	0	0	0	33.3	42.8	66.7	57.1
CORN	0	0	8.3	28.6	41.7	42.8	50	28.6
POTATOES	0	0	16.6	14.3	58.3	57.1	25	14.3
WHITE BREAD	0	42.8	16.6	28.6	58.3	28.6	25	0
COLOCASIA ESCULENTA (TALAS)	0	0	0	0	0	0	100	100
LEAFY VEGETABLES	0	71.4	28.6	28.6	63.1	0	8.3	0
MUNG BEAN SPROUTS	8.3	28.6	33.3	14.3	58.3	57.1	8.3	0
< 0.1 MG B1/100 G SUBSTANCE								
CHICKEN	0	0	50	71.4	50	28.6	0	0
MILK FISH	0	0	25	42.8	58.3	57.1	16.6	0
SALTED FISH	0	0	16.6	14.3	33.3	85.7	50	0
SOYBEAN CURD	16.6	42.8	66.7	57.1	16.6	0	0	0
CASSAVA	8.3	0	16.6	14.3	75	71.4	0	14.3
YAM	0	0	16.6	14.3	50	28.6	33.3	57.1
CRACKERS	0	14.3	0	28.6	75	57.1	25	0
VEGETABLES	50	85.7	25	14.3	16.6	0	8.3	0
FRUIT	33.3	42.8	50	42.8	16.6	14.3	0	0

+ = sucllinical pnp.
- = non-pnp.

TABLE 8.8 ABNORMAL NEUROLOGICAL SYMPTOMS (SUBCLINICAL PNP PATIENTS)

SYMPTOMS	% ABNORMALITY LOW INCOME (35 patients)	% ABNORMALITY MIDDLE & HIGH INCOME (7 patients)	% TOTAL ABNORMALITY (42 patients)	DURATION OF SYMPTOMS
Numbness/ tingling sensation	40	42.8	40.5	2 weeks - 3 years
Easy fatigability	34.3	42.8	35.7	3 months - 3 years
Muscle cramps	25.7	28.6	26.2	2 weeks - 2 years
Cold extremities	20	14.3	19.0	1 - 2 years
Profuse sweating	11.4	14.3	11.9	1 - 2 years
Oedema of foot	2.8	0	2.4	1 - 2 years ago
Irritability	2.8	0	2.4	1 - 2 years

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TABLE 8.9 ABNORMAL NEUROLOGICAL SIGNS (SUBCLINICAL PNP PATIENTS)

SIGNS	% ABNORMALITY LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	% TOTAL ABNORMALITY (42 patients)
CRANIAL NERVES	0	0	0
MOTOR FUNCTION			
Squat test	0	0	0
Walk on heels	0	0	0
Walk on toes	0	0	0
Paresis of dorsi-flexion of feet/ great toes	57.1	57.1	57.1
SENSORY FUNCTION			
Leg			
Touch (SW-test)	40	42.8	40.5
Pain/temperature	37.1	42.8	38.1
Vibration	5.7	14.3	7.1
Position	2.8	0	2.4
Arm			
Touch (SW-test)	20	28.6	21.4
Pain/temperature	17.1	14.3	16.7
Vibration	2.8	0	2.4
Position	0	0	0
Hypersensitive	2.8	0	2.4
TENDERNESS OF CALF MUSCLES	11.4	14.3	11.9
REFLEXES			
Ankle jerk			
sluggish	40	42.8	40.5
exaggerated	2.8	0	2.4
Knee jerk			
sluggish	31.4	28.6	30.9
exaggerated	2.8	0	2.4
Biceps tendon reflex			
sluggish	2.8	0	2.4
Triceps tendon reflex			
sluggish	5.7	0	4.8

TABLE 8.10 ELECTRONEUROMYOGRAPHIC FINDINGS (1)
(SUBCLINICAL PNP PATIENTS)

PROCEDURE	% ABNORMALITY LOW INCOME (35 patients)	% ABNORMALITY MIDDLE & HIGH INCOME (7 patients)	% TOTAL ABNORMALITY (42 patients)
PERONEAL MOTOR			
Latency time			
ankle	20	14.3	19.0
knee	8.7	0	7.1
Amplitude			
ankle	65.7	57.1	64.3
knee	45.2	42.8	52.4
MCV	0	0	0
POSTERIOR TIBIAL MOTOR			
Latency time			
ankle	0	0	0
knee	0	0	0
Amplitude			
ankle	0	0	0
knee	0	0	0
MCV	0	0	0
MEDIAN MOTOR			
Latency time			
wrist	0	0	0
elbow	0	0	0
Amplitude			
wrist	11.4	14.3	11.9
elbow	8.6	0	7.1
MCV	0	0	0

MCV = motor nerve conduction velocity

TABLE 8.11 ELECTRONEUROMYOGRAPHIC FINDINGS (2)
(SUBCLINICAL PNP PATIENTS)

PROCEDURE	% ABNORMALITY LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	% TOTAL ABNORMALITY (42 patients)
SURAL SENSORY (ORTHODROMIC)			
Distal latency time	14.3	14.3	14.3
Amplitude	25.7	28.6	26.2
MEDIAN SENSORY (ORTHODROMIC)			
Distal latency time	0	0	0
Amplitude	8.6	0	7.1
H-REFLEX (M.SOLEUS)			
Latency time	20	14.3	19.0
Amplitude	60	42.8	57.1
MUSCLES			
Anterior tibial			
Pos.sharp wave	57.1	57.1	57.1
Fibrillation	2.9	0	2.4
Reduced CMAP	40	0	2.4
Abd.poll.brevis			
Pos.sharp wave	25.7	28.6	26.2
Fibrillation	0	0	0
Reduced CMAP	11.4	0	9.5

CMAP = Compound muscle action potential
Pos. = positive
Abd.poll. = Abductor pollicis

TABLE 8.12 LABORATORY FINDINGS
(SUBCLINICAL PNP PATIENTS)

ITEM	TOTAL MEAN VALUE LOW INCOME (35 patients)	MIDDLE & HIGH INCOME (7 patients)	TOTAL MEAN VALUE LOW INCOME/MIDDLE & HIGH INCOME (42 patients)	NORMAL CONVENTIONAL UNIT
HAEMOGLOBIN	12.6 ± 1.3	13.8 ± 1.7	13.2 ± 1.4	12 - 18 g/dl
BLOOD GLUCOSE FASTING	79.8 ± 9.4	76.2 ± 10.5	78 ± 9.9	< 115 mg/dl
2 HOURS POST PRANDIAL	105.6 ± 6.5	103.7 ± 7.1	104.6 ± 6.7	< 140 mg/dl
SGOT	26.8 ± 12.9	25.8 ± 13.7	26.3 ± 13.2	7 - 40 millifunits/dl (37° C)
SGPT	26.7 ± 14.4	24.2 ± 15.5	25.4 ± 14.6	5 - 35 millifunits/dl (37° C)
CREATININE (SERUM)	1.03 ± 0.2	0.98 ± 0.3	1.0 ± 0.2	0.6 - 1.2 mg/dl
UREA (BLOOD)	16.4 ± 4.6	15.2 ± 4.8	15.8 ± 4.7	21 - 43 mg/dl
TOTAL PROTEIN (SERUM)	7.4 ± 0.4	7.6 ± 0.9	7.5 ± 0.6	6 - 8 g/dl
ALBUMIN (SERUM)	4.3 ± 0.5	4.4 ± 0.6	4.3 ± 0.5	3.5 - 5.5 g/dl
THIAMINE (BLOOD)	8.7 ± 1.5	9.4 ± 1.9	9.0 ± 1.8	11.3 - 47.8 mug/ml (Hyint and Houser, 1965)

SGOT = serum glutamic-oxaloacetic transaminase
SGPT = serum glutamic-pyruvic transaminase

CHAPTER 9

ELECTROPHYSIOLOGICAL EXAMINATION OF BERIBERI POLYNEUROPATHY

(Djoenaidi and Notermans)

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9.1 INTRODUCTION

Electrophysiological examination is essential for the diagnosis of polyneuropathy, especially in subclinical polyneuropathy and uncooperative patients, such as infants and young children. Moreover, clinical neurophysiological studies may provide some clues as to whether the pathological process involves the axon or the myelin sheath

To our knowledge, electroneuromyographic findings in beriberi polyneuropathy have never been described extensively. This study reports the electrophysiological evaluation of beriberi polyneuropathy in man and of experimentally induced thiamine deficiency in chickens (Djoenaidi and Notermans, 1990 b). It aims to evaluate the various abnormal electrophysiological findings providing a sensitive and very reliable measure of beriberi polyneuropathy By means of this evaluation it should be possible to establish which parameters might be useful in the diagnosis of polyneuropathy, especially in patients with thiamine deficiency. These findings also seem to be important for the therapeutic approach of these patients.

9.2 STUDY DESIGN AND METHODOLOGY

The subjects consisted of 68 low socio-economic, beriberi polyneuropathic patients admitted to the neurological department of the Dr. Soetomo Hospital, Surabaya, Indonesia, between January 1986 and June 1988

The diagnosis was arrived at as previously described (Djoenaidi and Notermans, 1990 a).

For the EMG study a Medelec MS92 was used. In the patients, nerve conduction studies were performed as recommended by Delisa et al. (1987). The H-reflex latency is judged on the basis of the nomogram of the simultaneous regression of H-wave latency on leg length and age (Delisa et al , 1987). Mean skin temperature of the appropriate limb was 33 °C (32 ° to 34 °C).

In an experimental situation, ten chickens (3 months old), who were fed with the same composition of diet as our low income beriberi polyneuropathic patients, developed beriberi polyneuropathy after about one month on such a diet. All the abnormal neurological symptoms disappeared after thiamine therapy Electrophysiological studies were only performed on the peroneal nerve, the sciatic nerve and on the gastrocnemial and peroneal muscles. Orthodromic sensory action potentials from the peroneal nerve were elicited by placing a concentric recording needle near the peroneal nerve in the ankle; for stimulation of the peroneal nerve a concentric needle was placed in the 1st phalanx of digit III. Nerve conduction studies were done with the concentric recording needle in the 1st phalanx of digit III and stimulation with the cathode in the ankle or sciatic notch, and the anode superior to it (see fig. 9 1 a, b). Studies were done in a room in which the temperature ranged from 32-34 °C.

9.3 RESULTS

The neurophysiological abnormalities in the 68 beriberi polyneuropathic patients are shown in the Tables 9.1 through 9.7. The electroneuromyographic findings of the experimental beriberi polyneuropathic chickens are depicted in Tables 9.8 through 9.11. In the Tables 9.12 and 9.13 a comparison is made of the abnormalities in nerve conduction parameters, late responses, and EMG.

Out of all the neurophysiological parameters assessed, the ones found to be most frequently and most severely abnormal were: the distal amplitude in peroneal motor nerve measurement (reduced in 92.7%), the H-reflex (prolonged in 89.6%) and electromyography in the leg muscles (pathologic in 85.3%)(see Tables 9.12 and 9.13), followed by motor nerve conduction velocity of the peroneal nerve (decreased in 60.2%), and the sural sensory nerve (decreased in 52.9%) (see Table 9.12). The latency of the F-wave was far less frequently abnormal (see Table 9.13).

A reduced distal amplitude of the peroneal motor nerve was the most frequently seen abnormality (up to 92.7%), followed by that of the posterior tibial motor nerve (73 5%), median motor nerve (10.3%), and ulnar motor nerve (10.3%) (see Tables 9.1 u/l 4).

The amplitude of the distal part of the motor nerve was most often found to be abnormal, followed closely by the distal latency time and the motor nerve conduction velocity (see Tables 9.1 u/l 4).

Considering the distal amplitude of the sensory nerve, the sural sensory nerve was affected most (52.9%), followed by the median sensory (32.3%) and ulnar sensory nerves (20.6%) (see Table 9.5). The distal amplitude of the sensory nerve was more frequently abnormal than the distal latency.

The legs were more severely affected than the arms and their distal parts more severely than the proximal ones. In experimentally induced beriberi in chickens, the following pathology was observed: EMG findings were most often abnormal in the gastrocnemius and peroneal muscles (100%); in all cases, F-wave latencies were prolonged (100%); slowing of the peroneal and sciatic motor nerve conduction was seen in 60%; the distal latency of the peroneal sensory nerve was prolonged in 60% of the cases. The motor nerve conduction velocity of the peroneal and sciatic nerves was less frequently affected (20-40%) (see Table 9.8 and 9.9). Clinically, the chickens showed an evident paresis of the limbs, which manifested itself in a disturbed gait (see Fig. 9.1 c).

9.4 DISCUSSION

Axonal neuropathy, which primarily affects the axon with either diffuse degeneration or dying back of its distal portion, is commonly seen in beriberi polyneuropathy or alcoholic polyneuropathy (Daube, 1980). Pathological changes in peripheral nerves in patients suffering from beriberi polyneuropathy are identical with those found in patients with alcoholic polyneuropathy (Notermans, 1984). The primary lesion in beriberi polyneuropathy is axonal degeneration, while changes in the myelin are secondary (Notermans, 1984).

The evoked action potentials of our patients showed to be most often and most severely abnormal in the distal amplitude of the peroneal nerve (up to 92.7%), followed by posterior tibial motor (73.5%), and median and ulnar motor nerve conduction velocity (both prolonged in 10.3% of the cases). The above mentioned findings were in accordance with the results of our study with experimental beriberi polyneuropathy in chickens.

Axonal neuropathies typically affect the longer axons first, resulting in early manifestations in the lower extremities. Nerves which are more susceptible to local trauma because of a superficial localisation are also more sensitive. Therefore, these disorders commonly become manifest initially as peroneal neuropathies.

A disorder associated with axonal destruction as in beriberi polyneuropathy is predominantly related to a reduction in amplitude of the evoked response at all sites of stimulation with relatively little slowing in conduction velocity (Lefebvre et al., 1979).

H-reflex latency appeared to be a sensitive indicator of the mild neuropathies associated with alcoholism (Kimura, 1983; Kimura, 1984; Lefebvre et al., 1979, Murai and Kuroiwa, 1973; Notermans, 1984). Lefebvre et al. (1979) found 63% of these late response latencies to be abnormal in the evaluation of alcoholic subjects. Willer and Dehen (1977) also considered H-reflex latencies as a sensitive test for early detection of alcoholic neuropathy. 89.6% of our patients showed an abnormality of their H-reflexes over the soleus muscle.

F-wave measurements are also useful in electrophysiological studies of patients and may be more sensitive than conventional motor nerve conduction velocity (MNCV) methods (Eisen et al., 1977; Panayiotopulous and Scaroakezis, 1977, Shahani and Young, 1980).

F-wave latency abnormalities were found in all of our experimentally induced beriberi neuropathic chickens. This is in contrast with the F-wave findings in our beriberi polyneuropathic patients. We found only 3.1 - 8.5% of the distal latencies of their F-waves to be abnormal. It can be postulated that polyneuropathies in chickens were particularly associated with prominent proximal pathology, whereas in man the distal segments were more severely affected.

The importance of sensory studies in metabolic neuropathies was stressed by Murai and Kuroiwa (1973) and Buchtal (1970), who suggested that large sensory fibers were often primarily involved.

Lefebvre et al. (1979) found a predominant involvement of sensory fibers, especially in the legs, in alcoholic neuropathy. 84% of their patients showed abnormalities of the sural conduction, but only 73% showed an abnormality of median and ulnar nerve sensory conduction. In alcoholic polyneuropathy, sensory potentials often demonstrate a considerable reduction, up to 50% of the average values (Notermans, 1984). Sensory nerve conduction may be more affected than motor conduction, and the degree of slowing in conduction velocity relates to the severity of the polyneuropathy (Kimura, 1984).

In 60% of our experimental beriberi polyneuropathic chickens, the distal latency of the sensory peroneal nerve conduction was abnormal, whereas in human beriberi polyneuropathy, 52.9% of the patients showed anomalies of the distal amplitude of the sural sensory nerve conduction, but only 32.3% and 20.6% in the median and ulnar sensory nerve conduction, respectively.

In electromyography, at voluntary muscle contraction the interference pattern is often significantly reduced and shows a diminished density (80.9%) in this form of beriberi polyneuropathy. Denervation activity, especially in the distal small muscles of the hand and foot, consisting of fibrillation potentials (58.8%) and positive sharp waves (82.3%), is also often found. In our experimentally induced beriberi polyneuropathy in chickens, positive spikes and complex repetitive discharges (100%) were always seen. Therefore, it may be concluded that the experimentally induced beriberi polyneuropathy in chickens provides a workable model for studying these forms of neuropathy in view of diagnosis and treatment.

9.5 SUMMARY

The diagnostic utility of electroneuromyography, including F-wave and H-reflex measurements, was studied in 68 patients with peripheral polyneuropathy due to nutritional deficiency of thiamine.

Out of all the electrophysiological evaluations assessed, reduced motor nerve action potentials, prolonged H-reflex latencies, denervation activity in electromyography and prolonged conduction velocities were the most frequently found abnormalities, followed by reduced sural nerve action potentials and, far less frequently, prolonged F-wave latencies. In experimental, thiamine deficiency provoked polyneuropathy in chickens, the prominent abnormalities were found in the leg muscles, such as F-wave pathology, reduction and prolongation of peroneal and sciatic motor nerve action potentials, and prolongation of the distal sensory peroneal nerve latencies.

TABLE 9.1 PERONEAL MOTOR NERVE

	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Latency time (Ankle)	77.9	8.02 msec	3.77 ± 0.62 msec
Latency time (Below Knee)	66.2	16.64 msec	10.79 ± 1.06 msec
Amplitude (Ankle)	92.7	709 μV	5100 ± 2300 μV
Amplitude (Below Knee)	91.2	585.8 μV	5100 ± 2000 μV
MCV	60.2	37.3 m/sec	52.6 ± 3.8 m/sec

MCV = Motor nerve conduction velocity

TABLE 9.2 POSTERIOR TIBIAL MOTOR NERVE

	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Latency time (Ankle)	51.5	6.39 msec	3.86 ± 0.6 msec
Latency time (Knee)	23.5	22.2 msec	12.05 ± 1.5 msec
Amplitude (Ankle)	73.5	1296.12 μV	5800 ± 1900 μV
Amplitude (Knee)	72.1	1215.38 μV	5100 ± 2200 μV
MCV	17.6	31.85 m/sec	47.2 ± 1.6 m/sec

TABLE 9.3 MEDIAN MOTOR NERVE

	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Latency time (Wrist)	14.7	8.06 msec	3.49 ± 0.34 msec
Latency time (Elbow)	5.9	21.96 msec	7.39 ± 0.69 msec
Amplitude (Wrist)	10.3	2615.2 μV	5100 ± 3000 μV
Amplitude (Elbow)	8.8	2616.6 μV	5100 ± 2700 μV
MCV	4.4	38.4 m/sec	57.7 ± 3.8 m/sec

TABLE 9.4 ULNAR MOTOR NERVE

	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Latency time (Wrist)	7.3	10.84 msec	2.59 ± 0.39 msec
Latency time (Above Elbow)	5.9	25.4 msec	8.04 ± 0.76 msec
Amplitude (Wrist)	10.3	1135.7 μV	5700 ± 2000 μV
Amplitude (Above Elbow)	8.8	1458.3 μV	5500 ± 1900 μV
MCV	4.4	26.13 m/sec	58.7 ± 5.3 m/sec

TABLE 9.5 SENSORY NERVE

NERVE	ORTHODROMIC	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Sural	Distal Latency	42.6	4.08 msec	2.08 ± 0.35 msec
	Amplitude	52.9	1.75 μV	5 μV
Median	Distal Latency	10.3	4.0 msec	2.84 ± 0.34 msec
	Amplitude	32.4	4.43 μV	10 μV
Ulnar	Distal Latency	14.7	3.96 msec	2.54 ± 0.29 msec
	Amplitude	20.6	1.75 μV	5 μV

TABLE 9.6 F-WAVE LATENCY

NERVE	SITE	% ABNOR-MALITY	MEAN ABNOR-MALITY	NORMAL VALUE
Posterior Tibial	Ankle	8.5	68.5 msec	47.7 ± 5.0 msec
	Knee	6.4	54 msec	39.6 ± 4.4 msec
Median	Wrist	2.5	54.5 msec	26.6 ± 2.2 msec
	Elbow	2.5	40 msec	22.8 ± 1.9 msec
Ulnar	Wrist	3.1	44.8 msec	27.6 ± 2.2 msec
	Elbow	3.1	35 msec	23.1 ± 1.7 msec

TABLE 9.7 MUSCLE

MUSCLE	POSITIVE SHARP WAVE (%)	FIBRILLATION POTENTIAL (%)	DECREASED CMAP AND OTHER ABN. FINDINGS (%)	NO CONTRACTION (%)
Anterior-Tibial	82.3	58.8	80.9	4.41
Gastrocnemius	80.9	57.3	82.3	2.9
A.P.B.	32.3	14.7	23.5	--
A.D.M.	22.1	10.3	14.7	--

CMAP = Compound Muscle Action Potential
ABN. = Abnormal
A.P.B. = Abductor Pollicis Brevis
A.D.M. = Abductor Digiti Minimi

TABLE 9.8 PERONEAL MOTOR NERVE (CHICKEN)

	% ABNORMALITY	NORMAL VALUE
Latency time (Ankle)	60	2.2 ± 0.3 msec
Latency time (Knee)	40	4.42 ± 0.56 msec
Amplitude (Ankle)	60	1500 ± 428.4 μV
Amplitude (Knee)	60	1530 ± 548.33 μV
MCV	20	45.3 ± 5.2 m/sec

TABLE 9.9 SCIATIC MOTOR NERVE (CHICKEN)

	% ABNORMALITY	NORMAL VALUE
Latency time (Sciatic Notch)	20	5.46 ± 0.6 msec
Amplitude (Sciatic Notch)	60	1505 ± 432.8 μV
MCV	40	63.71 ± 14.2 m/sec

TABLE 9.10 PERONEAL SENSORY/MUSCLE (CHICKEN)

NERVE/MUSCLE	% ABNORMALITY	NORMAL VALUE
Distal latency (Peroneal Nerve)	60	1.35 ± 0.19 msec
Distal amplitude (Peroneal Nerve)	0	6.5 ± 3.34 μV
Gastrocnemius and Peroneal Muscles	100	--

TABLE 9.11 F-WAVE LATENCY (CHICKEN) PARAMETERS

SITE	% ABNORMALITY	NORMAL VALUE
Ankle	100	13.06 ± 1.56 msec
Knee	100	12.22 ± 1.53 msec
Amplitude (Ankle)	0	295 ± 260.8 μV
Amplitude (Knee)	0	380 ± 407.7 μV

TABLE 9.12 COMPARISON OF NERVE CONDUCTION PARAMETERS

NERVE	% ABNORMALITY		
	DISTAL AMPLITUDE	DISTAL LATENCY	MCV
Peroneal motor	92.7	77.9	60.2
Posterior-Tibial Motor	73.5	51.5	17.6
Median Motor	10.3	14.7	4.4
Ulnar Motor	10.3	7.3	4.4
Sural Sensory	52.9	52.9	--
Median Sensory	32.3	10.3	--
Ulnar Sensory	20.6	14.7	--

TABLE 9.13 COMPARISON OF LATE RESPONSES AND EMG

NERVE / / MUSCLE	% ABNORMALITY		
	DISTAL LATENCY	DISTAL AMPLITUDE	MUSCLE
Posterior tibial (F-wave)	8.5	--	--
Median (F-wave)	2.5	--	--
Ulnar (F-wave)	3.1	--	--
H-reflex (Soleus)	88.2	89.7	--
Ant. Tib.	--	--	85.3
Gastrocnemius	--	--	85.3
A.P.B.	--	--	32.3
A.D.M.	--	--	22.1

Ant. Tib. = Anterior Tibial
A.P.B. = Abductor Pollicis Brevis
A.D.M. = Abductor Digiti Minimi

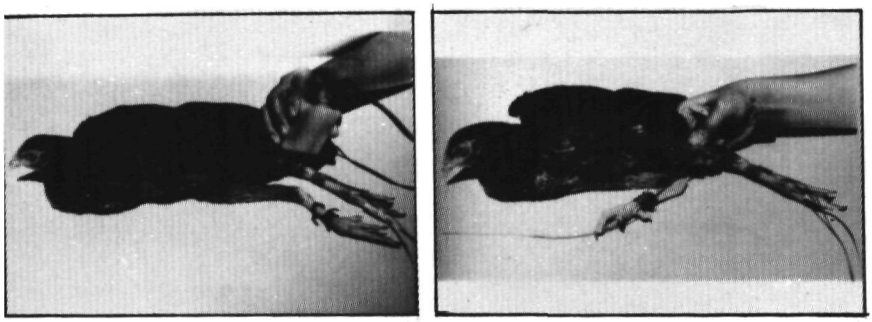

Fig. 9.1 a,b Placement of electrodes for stimulation (left) and recording (right).

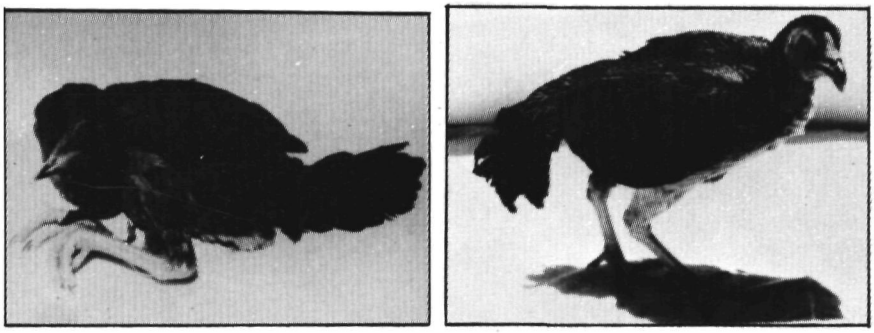

Fig. 9.1 c,d Photographs of a chicken with thiamine deficiency neuropathy (left) and the same chicken, recovered after TTFD treatment (right).

CHAPTER 10

GENERAL DISCUSSION

Incidence of clinical beriberi PNP

During the period of our study, the incidence rate of beriberi PNP in hospital cases in Surabaya was 3.9%. Compared with the results of Wadia, who found the disease in 41.8% of 67 malnourished patients admitted to a teaching hospital in Bombay in 1984, this is a rather low percentage. Also Chen et al. (1984), in China, reported, that 62.7% of the 429 peasants they examined suffered from beriberi.

An explanation for the low incidence of clinical beriberi PNP in our study may be that mild cases and the very poor patients may not be seen in hospital at all. They go to practicing nurses or buy medicine in small shops. Besides, the diagnosis may be overlooked since the symptoms and signs of mild cases are of minor nature Almost all of our cases (89.2%) suffered from severe to moderately severe beriberi PNP

The incidence rate of beriberi PNP in the period of August 1986 to August 1987 did not differ significantly from that found in 1989, i.e. 4.03% and 3.83%, respectively. This indicates that in our country (Indonesia) beriberi is probably endemic.

Prevalence of subclinical beriberi

The prevalence rate of subclinical beriberi PNP in the low income group was 66%. Hailemariam et al. (1985), in Jamaica, found subclinical thiamine deficiency in 7% of normal children and 36% of malnourished children on admission to hospital In groups of the settled !Kungsan, living in the Northern Kalahari desert of Namibia, Van der Westhuyzen et al. (1987) found that one-third of the men and 20% of the women had low red cell thiamine concentrations.

From the high prevalence rate of subclinical cases in the low income groups we may conclude, that most of these income group patients had an inadequate diet, especially concerning deficient thiamine intake. Analysis of the diets revealed, that they were usually rich in carbohydrate, whereas intake of fat and thiamine was low, protein was just sufficient. The total calorie intake was marginal. Carbohydrate rich and non-fat calories in the diet with low thiamine intake may provoke beriberi.

Clinical features

The clinical features of beriberi PNP are very much the same as in alcohol neuropathy, although not all authors (Denny-Brown, 1958; Bischoff, 1971; Behse and Buchtal, 1977) agree that alcohol neuropathy and beriberi are identical. That alcohol PNP does not result from the neurotoxic effect of alcohol was demonstrated by Strauss (1935) and Mayer (1966). Moreover, there are no convincing data from animal experiments to suggest that degeneration of peripheral nerves can be brought about by alcohol alone (Victor, 1984). Therefore, it is concluded that polyneuropathy in alcoholics is the result of a nutritional deficiency (Notermans, 1984; Victor, 1984).

A burning pain in the legs was the most frequent complaint in 13 dry beriberi cases reported by Mengistu and Maru (1979) This is in contrast with our findings and those of Chen et al. (1984) and Demeke and Habte-Gabr (1982), which did not include this

type of complaint. Patients with an acute breakdown of myelinated fibres tend to have pain more often and to a greater degree than patients with a more chronic form of nerve fibre degeneration (Dyck et al., 1971).

The neurological symptoms of our patients antedated many years before the PNP attack, indicating a chronic process.

Musculoskeletal symptoms such as knee pain, stiffness of the legs and muscular pain were found in latent thiamine deficiency (Demeke and Habte-Gabr, 1982). In our patients, there were no musculoskeletal complaints. This is in accordance with findings of other authors, such as Chen et al. (1984), and Mengistu and Maru (1979).

Mengistu and Maru (1979) found in their dry beriberi patients, that the senses of vibration and position were more affected than the touch sensation. In our patients, on the other hand, the touch sensation was found to be more affected than the vibration and position senses. Testing of the touch sensation, which evaluates the functioning of the slowly adapting fibres, is a more sensitive tool than the vibration test, in which the quickly adapting fibres are evaluated. A slowly adapting fibre continues its pulse response throughout the duration of the stimulus, whereas a quickly adapting fibre signals an on-off event. Results of position sense testing are less reliable, because this test requires complex overlapping and intermingling of different sensory units, as well as a great deal of cortical integration (Gelberman et al., 1983).

The "walk on heels" test seemed to be more reliable than the "squat" test, especially in the moderately severe cases. In beriberi PNP, the quadriceps muscles were later and less severely affected than the distal leg muscles, while the anterior tibial muscles were more involved than the gastrocnemius muscles. Failure of axon transport results in degeneration of vulnerable distal regions of long superficial or large diameter axons. Besides, the superficial location of the peroneal nerve makes it more susceptible to injury than the deep-seated tibial nerve.

Exaggerated knee and ankle jerks were found in only few of our beriberi PNP patients. Mengistu and Maru (1979), as well as Demeke and Habte-Gabr (1982), reported exaggerated deep tendon reflexes in their beriberi patients. Everett (1979) assumed the cause of it to be a multiple vitamin deficiency, and not just thiamine deficiency. Reduced ankle jerks in combination with normal knee tendon reflexes were the earliest signs of beriberi polyneuropathy in our subclinical patients. This is due to the distal leg muscles being earlier and more severely involved than the proximal ones.

Neurophysiological findings

Abnormalities in the F-response were frequently found in alcoholic patients (Lefebvre et al., 1979). This is in contrast with the findings in our beriberi PNP patients, in whom the latency of the F-wave turned out to be the least affected. The F-response will have a prolonged latency, if there is involvement of the motor axons (Shahani and Young, 1980). Blackstock et al. (1972) found in their alcoholic patients that the large afferent fibres were affected, whereas the large efferent motor axons functioned normally.

CHAPTER 11

SUMMARY AND CONCLUSIONS

The aim of this study has been to determine, whether the nutritional polyneuropathy, as seen in patients from low income groups in and around Surabaya, could be attributed to thiamine deficiency.
A detailed literature overview was given about beriberi and thiamine metabolism.
In the Department of Neurology, Dr. Soetomo Hospital, Surabaya, there was noticed an increasing trend in polyneuropathy (PNP) patients in the years 1981-1989, which could not be attributed to the common causes such as diabetes mellitus, uraemia, leprosy, Guillain Barré syndrome, alcoholism or toxic substances. The tentative diagnosis of beriberi PNP was made.
It was proved ex juvantibus, that the nutritional PNP in the patients included in our study was indeed caused by thiamine deficiency. An experimental study in chickens verified our hypothesis that thiamine deficiency per se can be the cause of nutritional polyneuropathy.
Since in the first phase of the study biochemical tests were not available locally, we repeated our investigations in patients when blood thiamine determination could be carried out in Surabaya. The test results showed, that all suspected patients had low blood thiamine levels.
The occurrence of beriberi cardiomyopathy and the existence of subclinical beriberi polyneuropathy further support our hypothesis.
The neurophysiological findings in our patients were typical of axonal degeneration and support the notion that beriberi PNP caused a distal axonopathy.

There has been an extensive investigation into the dietary habits of the patients, by means of a specific questionnaire. The data obtained from this survey showed, that most of the patients belonged to the low income groups. The majority lived in Surabaya, and young men were affected more than older men and women. The mean number of family members was about 5 (ranging from 1 to 11). The staple food was government-distributed milled rice. Foodstuffs other than the staple food were consumed irregularly. The median calorie intake was just sufficient and the diet consisted mainly of carbohydrates, with little fat and a reasonable amount of protein. The median intake of thiamine appeared to be low. As thiamine requirement depends mainly on the amount of non-fat calories in the diet, a carbohydrate-rich diet, deficient in thiamine, may provoke thiamine deficiency.

Regarding the incidence rate of hospital cases of beriberi polyneuropathy in the low income groups, it was found that this did not change over the years indicating that beriberi is probably endemic in Indonesia. From the high prevalence rate of subclinical beriberi polyneuropathy in the community, it was concluded, that most of our low income patients live on diets that are so inadequate, that beriberi is getting a chance to develop again, just as happened in the past century.

The clinical picture of clinical and subclinical beriberi polyneuropathy and wet beriberi has been described in the preceding chapters. A tingling sensation in the distal parts of the extremities, easy fatigability, and muscle cramps were the earliest

symptoms of clinical and subclinical beriberi PNP. The "walk on heels" test turned out to be more reliable than the "squat" test in moderately severe beriberi PNP. Slight paresis of the dorsiflexion of the great toes, slight disturbances of the senses of touch, pain, and temperature in the distal parts of the legs, and depressed ankle jerks were the most frequent abnormal signs in subclinical beriberi PNP.
Acute heart failure (cardiomegaly with heart failure) of obscure origin, non-specific changes in the electrocardiogram, dependent oedema, elevated venous pressure, and polyneuropathy were the main signs of wet beriberi which were often found in young patients with an inadequate diet.

The study included various neurophysiological examinations. Evaluation of the results shows, that neurophysiological examination can be a sensitive and reliable tool in establishing the extent of polyneuropathy in patients suffering from beriberi. Reduction of the distal amplitude of the peroneal motor nerve, reduced amplitude of the H-reflexes, and denervation activity in electromyography of the distal leg muscles were the earliest abnormal neurophysiological findings in our clinical and subclinical beriberi PNP patients.

We have come to the conclusion, that in Indonesia beriberi is probably endemic, and it is indeed a national health problem, especially for the low income groups and is usually encountered among young people. Beriberi PNP and probably wet beriberi are more common than expected and usually not diagnosed as such. The problem is serious enough to warrant a public health measure.

CHAPTER 12

RECOMMENDATIONS

To all physicians in Indonesia; please be aware, that beriberi polyneuropathy may occur, especially in patients belonging to the lower income groups.
All patients with acute heart failure of obscure origin should have routine intravenous administration of thiamine, in view of the harmless nature of this drug and the high mortality of untreated beriberi cardiomyopathy.
Wernicke's encephalopathy should be considered, when patients develop unexplained confusion, obtundation, or sudden coma while receiving long-term intravenous feeding. It should be noted, that small daily doses of thiamine may not protect patients from developing thiamine deficiency while on intravenous hyperalimentation regimens.

To the government, which rations or sells the overmilled rice; reduction of milling will be beneficial. Prolonged storage of the rice should be avoided as much as possible, especially if the stored rice is not well protected against humidity.

To the nutritional health education authorities; people in the low income groups should be made aware, that their complaints may be caused by thiamine deficiency, and that they should not hesitate to go to their general practitioner or to hospital for treatment. A greater awareness can be created by means of informative brochures, lectures, television programmes, and so on.
People should also be instructed on how to prevent excessive thiamine loss when preparing their rice They should not wash the rice vigorously until the washing is clear, washing it twice is sufficient. They should not rub the rice, and the cooking time should be kept at a minimum.
Moreover, people should be advised to include inexpensive, thiamine-rich foods in their diets, such as rice bran, tempe (fermented soybeans), mung beans, and cow peas.

Recommendations for research
The findings of this study will have profound policy implications if it can be shown that the prevalence in East Java province or other areas of Indonesia is equally high among the apparently healthy or if polyneuropathy in other hospitals or Health Centres also prove to be due to thiamine deficiency. A community-based survey among representative population groups as well as institution-based studies are therefore strongly recommended. Special attention should be given to pregnant and lactating women, since they are most at risk, if beriberi is endemic.

SAMENVATTING EN CONCLUSIES

In dit proefschrift is getracht de bewijsvoering te leveren van de stelling, dat deficiëntie-polyneuropathie, zoals die voorkomt bij mensen behorend tot de lage inkomensgroepen in Surabaya en omgeving, kan worden toegeschreven aan thiamine-deficiëntie.

Een uitvoerig overzicht wordt gegeven van de literatuur over beriberi en thiamine-metabolisme.

In de jaren 1981-1989 wordt op de afdeling Neurologie van het Dr. Soetomo Ziekenhuis in Surabaya, een toename van het aantal patiënten met polyneuropathie waargenomen, waarbij de polyneuropathie niet kon worden toegeschreven aan de veel voorkomende oorzaken van polyneuropathie zoals: diabetes mellitus, uremie, lepra, syndroom van Guillain Barré, alcoholisme of toxische stoffen. Op grond van bovengenoemde redenen wordt de waarschijnlijkheidsdiagnose beriberi-polyneuropathy gesteld.

Bewezen is, dat de deficiëntie-polyneuropathie bij de voor deze studie onderzochte patiënten inderdaad door thiamine- deficiëntie veroorzaakt wordt, terwijl onze hypothese, dat thiamine-deficiëntie de enige oorzaak was, door experimenteel onderzoek bij kippen onderbouwd werd.

Daar in eerste instantie de mogelijkheden voor biochemisch onderzoek ter plaatse niet voorhanden waren, is het patiëntenonderzoek herhaald, zodra de bepaling van het thiamine gehalte in het bloed in Surabaya kon geschieden. Alle patiënten, bij wie thiamine-deficiëntie vermoed werd, bleken lage thiamine-bloed-spiegels te hebben.

Ook de aanwezigheid van beriberi-cardiomyopathie en subklinische beriberi-polyneuropathie (beriberi-PNP) bij de genoemde patiënten bevestigde onze hypothese.

De neurofysiologische bevindingen bij de onderzochte patiënten duidden op een axonale denervatie en bevestigden ons in onze overtuiging, dat beriberi-PNP een uiting is van een distale axonopathie.

Door middel van een uitvoerige vragenlijst werden gegevens omtrent de eetgewoonten van de patiënten verzameld. Op grond van deze gegevens kon worden vastgesteld, dat de meeste patiënten tot de lagere-inkomensgroepen behoorden. De meesten woonden in Surabaya en omgevig. Jonge mannen bleken vaker aan deze ziekte te lijden dan oudere mannen en vrouwen. De gezinnen waarvan patiënten deel-uitmaakten bestonden gemiddeld uit 5 personen (variërend van 1 tot 11). Het hoofdvoedsel was gepelde rijst, welke door de regering wordt verstrekt. De gemiddelde hoeveelheid calorieën in de dagelijkse voeding was net voldoende. Men at voornamelijk voedsel dat rijk is aan koolhydraten, arm is aan vet, en een redelijk eiwitgehalte heeft. De gemiddelde thiamine-opname bleek laag te zijn. Daar de behoefte aan thiamine voornamelijk van de hoeveelheid van non-vet calorieën in de voeding afhangt, kan koolhydraatrijke voeding een te kort aan thiamine, en zo thiamine-deficiëntie teweegbrengen.

De incidentie van de klinische gevallen van beriberi-PNP veranderde in de loop van de tijd niet en dit onderbouwt de mening dat beriberi waarschijnlijk endemisch in Indonesië voorkomt. Uit de hoge prevalentie van subklinische beriberi-PNP in de lage-inkomensgroepen in de gemeenschap, kunnen we concluderen dat blijkbaar het menu van een groot deel van deze inkomensgroep zo inadequaat is dat beriberi frequenter voorkomt, welke situatie lijkt op die van het begin van de deze eeuw.

Wat betreft het klinische beeld van klinische en subklinische beriberi-PNP en van natte beriberi, kwamen wij tot de volgende bevindingen.
Tintelingen in de distale gedeelten van de ledematen, vermoeibaarheid en spierkrampen waren de vroegste verschijnselen van klinische en subklinische beriberi-PNP.
De "hak-loop" proef bleek betrouwbaarder dan de "hurk" proef bij matig ernstige beriberi-PNP.
Lichte parese van de dorsale flectoren van de grote tenen, lichte aandoeningen van tast-, pijn- en temperatuurzin en verlaagde achillespees-reflexen waren de meest geconstateerde afwijkingen bij subklinische beriberi-PNP.
Acute hartinsufficiëntie (hartvergroting met insufficiëntie) door onbekende oorzaak, aspecifieke veranderingen in het electrocardiogram, oedeem, verhoogde veneuze druk en polyneuropathie waren de voornaamste tekenen van natte beriberi, dikwijls geconstateerd bij jonge mensen met een inadequaat voedingspatroon.

De neurofysiologische bevindingen worden hier eveneens beschreven. Het doel van de verschillende onderzoeken was, te bepalen in hoeverre neurofysiologische bevindingen een bijdrage kunnen leveren aan het vaststellen van beriberi-PNP.
Een drietal bevindingen bleek al in een zeer vroeg stadium van klinische en subklinische beriberi-PNP afwijkend te zijn, te weten: verminderde distale amplitude van de perifere beenzenuwen, verlaagde amplitude van de H-reflexen, en denervatie-activiteit in het EMG van de distale beenspieren.

Concluderend kan gesteld worden, dat beriberi waarschijnlijk endemisch voorkomt in Indonesië en dat dit een nationaal gezondheidsprobleem is, dat vooral bij de lagere-inkomensgroepen, en vooral bij jonge mensen wordt waargenomen Beriberi-PNP en waarschijnlijk natte beriberi komen vaker voor dan algemeen gedacht wordt en deze aandoening wordt nogal eens ten onrechte niet gediagnosticeerd. De ernst van het probleem lijkt het nemen van maatregelen van overheidswege te rechtvaardigen.

IKHTISAR DAN KESIMPULAN

Tujuan penelitian kami ini untuk menerangkan apakah polineuropati nutrisional dari kelompok masyarakat yang berpenghasilan rendah di Surabaya dan sekitarnya disebabkan oleh kekurangan tiamin.
Telah dibahas peninjauan kepustakaan yang luas dan terperinci mengenai beriberi dan metabolisme tiamin.
Pada tahun 1981-1989, di Lab. Ilmu Penyakit Saraf, Rumah Sakit Dr. Soetomo, Surabaya, terdapat kecenderungan kenaikan polineuropati yang tak disebabkan oleh penyebab umum seperti diabetes mellitus, uremia, penyakit kusta, sindroma Guillain-Barré, alkoholisme atau zat-zat yang mengandung racun (toksik). Atas dasar tersebut di atas dibuat perkiraan diagnosis polineuropati beriberi.
Telah dibuktikan secara ex juvantibus bahwa polineuropati nutrisional yang kami selidiki memang betul disebabkan oleh kekurangan tiamin. Penelitian dengan ayam menguji hipotesis kami bahwa kekurangan tiamin adalah satu-satunya penyebab dari polineuropati nutrisional.
Karena pada tahap awal ditempat kami tak dapat dilakukan tes-tes biokimiawi, maka penelitian dari penderita diulang lagi setelah penentuan kadar tiamin darah dapat dilakukan di Surabaya Ternyata semua penderita yang dicurigai mempunyai kadar tiamin darah yang rendah.
Terdapatnya kardiomiopati beriberi dan adanya polineuropati beriberi subklinikal lebih memperkuat hipotesis kami.
Hasil pemeriksaan neurofisiologik dari penderita kami adalah khas degenerasi aksonal dan menyokong perkiraan bahwa polineuropati beriberi disebabkan oleh aksonopati distal

Dengan perantaraan daftar pertanyaan telah dilakukan penyelidikan luas mengenai kebiasaan makan dari penderita-penderita. Data yang diperoleh pada penelitian ini menunjukkan bahwa sebagian besar penderita kami termasuk kelompok masyarakat berpenghasilan rendah Kebanyakan dari mereka bertempat tinggal di Surabaya dan pria muda yang paling banyak terkena dibandingkan dengan pria dan wanita yang lebih tua. Jumlah rata-rata dalam sekeluarga sekitar lima orang (berkisar antara 1-11). Makanan pokoknya adalah beras giling yang disalurkan oleh pemerintah. Bahan makanan selain makanan pokok dimakan secara tak teratur. Jumlah rata-rata energi yang dimakan adalah cukup dan mengandung tinggi hidrat arang, rendah lemak dan protein yang memadai Jumlah rata-rata tiamin yang dimakan ternyata rendah. Karena kebutuhan tiamin sebagian besar tergantung pada banyaknya kalori non-lemak, maka makanan yang mengandung tinggi hidrat arang dan sedikit tiamin, dapat menyebabkan beriberi.

Angka kejadian dari polineuropati beriberi yang masuk rumah sakit tak berobah dari tahun ke tahun, dan ini menunjukkan bahwa beriberi di Indonesia kemungkinan besar endemis. Dari angka prevalensi yang tinggi dari polineuropati beriberi subklinikal pada kelompok masyarakat berpenghasilan rendah dapat diambil kesimpulan bahwa kebanyakan dari kelompok masyarakat ini, nilai gizi makanannya begitu tidak mencukupi sehingga beriberi dapat timbul lagi, seperti yang telah terjadi pada abad yang silam.

Gambaran klinik dari polineuropati beriberi klinik, subklinikal dan beriberi basah telah dibahas dalam bab yang terdahulu.
Rasa kesemutan (gringgingan) dari bagian distal dari anggota gerak badan, mudah lelah dan kram otot adalah gejala terdini dari polineuropati beriberi klinikal dan subklinikal. Tes "jalan diatas tumit" ternyata lebih dapat dipercaya dari pada tes "jongkok" pada polineuropati beriberi yang agak hebat.
Paresis ringan dorsifleksi ibu jari kaki, gangguan ringan rasa raba, nyeri, suhu pada bagian distal tungkai dan reflek pergelangan kaki yang rendah adalah tanda-tanda abnormal yang paling sering terdapat pada polineuropati beriberi subklinikal. Kegagalan jantung akut (pembesaran jantung dengan kegagalan jantung) dengan penyebab yang tak jelas, edema, tekanan vena meningkat dan polineuropati adalah tanda-tanda utama beriberi basah, yang sering terdapat pada penderita usia muda dengan nilai gizi makanan yang tak memadai.

Pada penelitian ini termasuk macam-macam pemeriksaan neurofisiologik. Penilaian dari hasil ini menunjukkan bahwa pemeriksaan neurofisiologik ini dapat sebagai tolok ukur yang peka dan handal dalam menentukan betapa beratnya polineuropati pada penderita beriberi.
Penurunan amplitudo distalis dari saraf motorik peroneus, penurunan amplitudo reflek-H dan aktivitas denervasi pada pemeriksaan elektromiografi dari otot tungkai bawah adalah kelainan neurofisiologik abnormal terdini pada penderita polineuropati beriberi klinikal dan subklinikal

Kita sampai pada kesimpulan bahwa di Indonesia beriberi kemungkinan besar endemis dan sungguh-sungguh merupakan masalah kesehatan nasional, khususnya untuk kelompok masyarakat berpenghasilan rendah dan lazimnya pada kelompok dewasa muda. Polineuropati beriberi dan kemungkinan beriberi basah lebih banyak terdapat dari pada yang kami perkirakan dan kebanyakan salah diagnosis. Masalah ini sangat gawat dan perlu mendapat perhatian dalam bidang kesehatan masyarakat.

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Annex 1

NUTRITIONAL POLYNEUROPATHY SURVEY

Name	:	Date of visit to the	
Sex (M/F)	:	outpatient clinic	: .....
Age	:		
Present address	:	Number of outpatient	
* Since when	:	clinic card	: .....
* Regency	:		
* Subdistrict	:	Date of admittance	: .....
Place of birth	:	Date of inpatient	
* Regency	:	clinic card	: .....
* Subdistrict	:	Interviewer	: .....

I. MAIN AND ADDITIONAL OCCUPATION OF ALL WORKING MEMBERS OF THE HOUSEHOLD

fill in: ..months/year; ..wks/months; ..days/wks; ..season/whole year

Name : .....
Family no. : .....

Occupation	Main	Additional	Main	Additional
FARMER				
1. Land owner	....	....	....	....
2. Rents land	....	....	....	....
3. "Tenant" (Share-cropping)	....	....	....	....
4. Permanent labourer	....	....	....	....
5. Seasonal labourer	....	....	....	....
PLANTATION				
6. Owner	....	....	....	....
7. Permanent labourer	....	....	....	....
8. Seasonal labourer	....	....	....	....
FISHERY				
9. Owner of boat	....	....	....	....
10.Rents the boat	....	....	....	....
11."Tenant"(bagi hasil)	....	....	....	....
12.Permanent labourer	....	....	....	....
13.Seasonal labourer	....	....	....	....
TRADING, BUSINESS				
14.Owner	....	....	....	....
15.Permanent labourer	....	....	....	....
16.Seasonal labourer	....	....	....	....
17.Permanent petty trader	....	....	....	....
18.Seasonal petty trader	....	....	....	....
SALT INDUSTRY				
19.Own business	....	....	....	....
20.Permanent labourer	....	....	....	....
21.Seasonal labourer	....	....	....	....
GOVT. SERVICE				
22/23. Group I :	....	....	....	....
24/25. Group II :	....	....	....	....
26/27. Group III :	....	....	....	....
REGIONAL GOVT. SERVICE				
28.Paid :	....	....	....	....
29.Not Paid :	....	....	....	....
OTHERS				
30.Armed forces/police	....	....	....	....
31.	....	....	....	....

II. **HOUSEHOLD COMPOSITION**
Nuclear family

No.	Name	Family Relation	Age	Sex	Code No.	Married/ unmarried	At Home Y/N	Highest education attained	Still at school Y/N	Occupation at present				
										Main	Addit.	Donation	None (how long)	Income per month
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														

III. INFORMATION ON DIET OF THE FAMILY

1. Food pattern of the day

Type of meals	Time of serving	What foods?
breakfast lunch dinner in between meal		

Instruction for interviewer:
Note down all types of food consumed, for instance
* rice, maize + tempe + sambal
* rice + spinach soup + sambal

2. Food pattern throughout the year

Main item	What season	Bought/own produced/ both	Price	Type	How Cooked
Unmixed: * rice * maize * cassava (fresh) * dried cassava Mixed: * rice - maize * rice-fresh cassava * rice-dried cassava * maize-cassava-rice * sukun *sukun+fresh(or dried) * cassava * sukun + rice/maize					

3. Complementary food

Type of food	What season	Bought/own produced/both
Roots : singkong talas Tubers: ubi		

3a. Is there any change of the food pattern/habit throughout the year or the passing years :

4. Side dishes

Type of food	Frequency of consumption					
	>1x p.day	<1x p.day	>3x p.wk	<3x p.wk	seldom	never
tahu, tempe						
(dried) pulses or nuts						
salted/dried fish						
fresh fish						
meat						
eggs						
sambal (trasi)						

5. Vegetables

Type of vegetables	Frequency of consumption					
	>1x p.day	<1x p.day	>3x p.wk	<3x p.wk	seldom	never
Green leafy vegetables						
.....						
.....						
.....						
Other vegetables						
...						
...						
...						

IV. HOUSING AND ENVIRONMENT SANITATION

1. House: Own: ...(1) Rented: ...(2) Lives with family: ...(3)
2. Walls: Bamboo (gedeg): ...(1) Bricks : ...(4)
   Wood: : ...(2) Other (mention) : ...(5)
   Half bricks : ...(3)
3. Roof: Thatched (sirap): ...(1) Tiles : ...(3)
   Corrugated iron : ...(2) Other (mention): ...(4)
4. Floor: Soil : ...(1) Cement : ...(3) Others: ...(5)
   Bamboo/wood : ...(2) Brick/Tiles : ...(4)
5. Number of rooms: ...
6. Kitchen: Separate: ...(1) Cooks outside, open space: ...(3)
   With bed/living room: ...(2) One for whole compound: ...(4)
7. Stable: None : ...(0) Stay outside, open space: ...(3)
   Not separate : ...(1) One for whole compound : ...(4)
   Separate : ...(5)
8. Windows: None in the whole house: ...(0)
   In every room : ...(1)
   Only in 1 living room : ...(2)
9. Source of light: Electricity: ...(1) Oil lamp: ...(3)
   Petromax : ...(2) Others : ...(4)
10. Source of drinking/cooking water:
    Spring: ...(1) Well: ...(3) Others: ...(5)
    River : ...(2) Tap water: ...(4)

11. Garbage disposal:
River: ...(1) Garden: ...(3) Garbage hole: ...(5)
Sea : ...(2) Field : ...(4) Burnt: ...(6) Others: ...(7)

12. Excreta disposal:
River: ...(1) Garden: ...(3) Public latrine: ...(5)
Sea : ...(2) Field : ...(4) Own latrine : ...(6)
Others : ...(7)

13. Properties:	No (0)	Yes (1)
1. Table/Chairs	...	...
2. Cupboard	...	...
3. Bed	...	...
4. Sewing machine	...	...
5. Radio	...	...
6. Tape recorder	...	...
7. TV	...	...
8. Clock	...	...
9. Sideboard	...	...
10. Horse-cart	...	...
11. Bicycle	...	...
12. Motorcycle	...	...
13. Car	...	...
14. Others: e.g. Jewelry, Becak	...	...

V. ANAMNESIS

* When do you suffer from this illness?
* Is the onset acute, subacute, or chronic?
* Do you feel heavy in the limbs or quickly fatigued or do you have difficulty in walking?
* Feeling of slackness in the knee joints and feet?
* Do you feel paraesthesia when squatting or sitting cross-legged?
* Do you feel stiffness and cramps in the muscles?
* Do you suffer from palpitation or exertional dyspnea?
* Past or present illness:
  - Fever?
  - Diabetes mellitus?
  - Kidney disease?
  - Other disease?
* What kind of drugs do you take, or are you in contact with insecticides?
* Date of last menstruation?
  - Pregnant or puerperium?
* Are you an alcoholic?
  - What kind of liquor do you drink?
  - How much do you drink a week?

VI. STATUS INTERNUS

General Clinical Parameter
* Body weight ...kg, Height ... cm
* Blood Pressure: ....
* Pulse: ....
* Face (puffy appearance): ....
* Oedema along inner surface of the tibia: ....
* Painful on pressure of the muscle: ....

Cervical Region
* Venous enlargement: ....
* Enlargement of lymph glandulae: ....

Heart
* Inspection: Ictus location at....., enlarged.....
* Palpation: Location of ictus at .....
* Percussion : The border of the heart: .....
* Auscultation :
  - Rhythm: .....
  - Heart sound: .....
  - Murmur: .....

Lungs

Liver/spleen

VII. STATUS PSYCHIATRICUS

Intelligence :
Thought :
Orientation :
Emotion & affect :

VIII. STATUS NEUROLOGICUS

General :
* Consciousness .....

Tonus :	Upper extremities	Lower extremities
* Flaccid	..../....	..../....
* Spastic	..../....	..../....
* Normal	..../....	..../....

Cranial nerves (total score = 20)

DATE / SCORE						
N III/IV/VI (-5)						
N VII (-5)						
N VIII (-5)						
N IX/X (-5)						
Total score						

Reflexes (total score = 18)

DATE / SCORE						
A T R						
K T R						
B T R						
T T R						
Total score						

Note:

ATR : Achilles Tendon Reflex	Normal	0
KTR : Knee Tendon Reflex	Decreased	-3
	Negative	-5
BTR : Biceps Tendon Reflex	Normal	0
TTR : Triceps Tendon Reflex	Decreased	-2
	Negative	-4

Sensory function (total score = 10)

	DATE / SCORE						
LEG	Touch (S-W test)						
	Vibration						
	Pain						
	Temperature						
	Deep						
ARM	Touch (S-W test)						
	Vibration						
	Pain						
	Temperature						
	Deep						
	Total score						

Note:

S-W = Semmes-Weinstein	Normal	0
	Decreased	-0.5
	Negative	-1

Motor function (LEG) (total score = 32)

PROCEDURE	Score / Date												
	Grade	L	R	L	R	L	R	L	R	L	R	L	R
Flexion artic coxae	V : -8 IV : -7 III : -6 II : -4 I : -2 0 : 0												
Extension artic coxae	V : -8 IV : -7 III : -6 II : -4 I : -2 0 : 0												
Flexion artic genu	V : -2 IV : -1.5 III : -1 II : -0.5 I : -0.25 0 : 0												
Extension artic genu	V : -4 IV : -3 III : -2 II : -1 I : -0.5 0 : 0												
Dorsal flexion of the foot	V : -4 IV : -3 III : -2 II : -1 I : -0.5 0 : 0												
Plantar flexion of the foot	V : -2 IV : -1.5 III : -1 II : -0.5 I : -0.25 0 : 0												
Flexion of the toes	V : -2 II : -1 I : -0.5 0 : 0												
Extension of the foot	V : -2 II : -1 I : -0.5 0 : 0												
Total score													

Motor function (ARM) (total score = 20)

PROCEDURE	Score / Date												
	Grade	L	R	L	R	L	R	L	R	L	R	L	R
Abduction upper arm	V : -4 IV : -3 III : -2 II : -1 I : -0.5 0 : 0												
Adduction upper arm	V : -4 IV : -3 III : -2 II : -1 I : -0.5 0 : 0												
Flexion artic cubiti	V : -2 IV : -1.5 III : -1 II : -0.5 I : -0.25 0 : 0												
Extension artic cubiti	V : -4 IV : -3 III : -2 II : -1 I : -0.5 0 : 0												
Flexion of the fingers	V : -2 II : -1 I : -0.5 0 : 0												
Extension of the fingers	V : -4 II : -3 I : -2 0 : 0												
Total score													

NOTE
Grade V : Complete paralysis (no visible movement)
Grade IV : Traces of contraction
Grade III : Active movements not against gravity
Grade II : Active movements against gravity
Grade I : Active movements against resistance
I-, I and I+ against slight,moderate and strong resistance
Grade 0 : normal power

TOTAL SCORES

	Score / Date					
Cranial nerves						
Reflexes						
Sensory function						
Motor function						
Total score						

NOTE : NORMAL FUNCTION:

Cranial nerves	20 points
Reflexes	18 points
Sensory function	10 points
Motor function	52 points
Total	100 points

Cerebellum
Extrapyramidal system
Autonomic nervous system
* Perspiration
* Incontinentia urinae/alvi
* Retentio urinae
* Obstipation

IX. ELECTRONEUROMYOGRAPHIC EXAMINATION

Amplitude distal latency
Peroneal nerve:
Posterior tibial nerve:
Median nerve:
Ulnar nerve:
SNAP (Sensoric Nerve Action Potentials)
Sural nerve:
Median nerve:
Ulnar nerve :
H-REFLEX
Soleus muscle :
EMG
M. Anterior tibial

X. LABORATORY EXAMINATION:

Blood sedimentation rate
Haemoglobin
Leukocytes
Differential count
Serum creatinine
Blood ureum nitrogen
Fasting blood sugar
2 Hours post prandial
SGOT (serum glutamic-oxaloacetic transaminase)
SGPT (serum glutamic-pyruvic transaminase)
Serum total protein
Serum albumin
Cerebrospinal fluid (if necessary)

Annex 2

BERIBERI POLYNEUROPATHY SURVEY

Date of interview	:	If unemployed :	
Name	:	Job of your husband/	
Sex (M/F)	:	wife/income per month	.
Age	:	Job of your father/mother/	
Present address	:	relation/income per month	:
Place of birth	:	Domicile	
Occupation	:	Rent a room	.
Income or pocket-money or		Boarding house	:
housekeeping money per		Dorm	:
month	:	Own house	:
		Name of the interviewer	:

I. AUTOANAMNESIS

1. Do you feel pins and needles or numbness of the fingers or toes or palm/plantar side of the foot? .....
   Since when? Which is more severe the foot or the hand? .....
2. Do you feel paraesthesia when squatting? .....
   Since when? After how many minutes squatting do you feel the paraesthesia? .....
3. Do you feel paraesthesia when sitting on the floor with legs crossed? .... Since when? After how many minutes cross-legged do you feel the paraesthesia? .....
4. Do you suffer from cramps in the gastrocnemius muscles or feet, especially during sleep at night? .....
5. Do you suffer from glove-stocking sensation? .....
6. Have you ever had oedema of the feet, ankles or lower legs? Since when?
7. Do you suffer from unusual fatigue or malaise? .....
8. Forgetfulness? Increased irritability? Loss of interest in daily tasks or disorderly thinking? .....
9. Do you feel heavy or quickly fatigued or weak in the legs when running or doing a sport? .....
10. Do you suffer from shortness of breath when going upstairs or palpitation after walking? .....
11. Do you awake at night due to shortness of breath? .....
12. How many pillows do you use when sleeping to prevent shortness of breath? ..... Do you suffer from orthopnea? .....
13. How many times do you urinate at night (nycturia)? .....
14. What is your hobby? Sprinter? Lifter? Others? .....
15. Are you an alcoholic? What kind of liquor do you drink? How many glasses do you drink a week? .....
16. Do you smoke? Have you ever smoked marihuana? .....
17. Did you suffer from fever before the attack? Diabetes mellitus? Kidney disease? Morbus Hansen? Others? .....
18. What kind of traditional medicine do you often take?.....
    Do you take antacids? Contact with insecticides? .....
19. How many times do you eat a day? .....
    Do you often consume instant noodles or soft drinks? .....
20. How many hours do you work or study a day? .....
    How many hours do you sleep a day? .....

HETEROANAMNESIS (FROM:.....) (FOR CHILDREN)

Does he/she suffer from obstipation? .... Vomiting? .... Fretfulness? .....
Loud piercing crying? .....Incessant crying? ..... Thin plaintive whining or aphonia? ..... Oliguria? ..... Cyanosis? .....Dyspnea? .....
Oedema? ..... Convulsions? .....

II. HOUSEHOLD COMPOSITION
Nuclear family

No.	Name	Family Relation	Age	Sex	Code No.	Married/ unmarried	At Home Y/N	Highest education attained	Still at school Y/N	Occupation at present				
										Main	Addit.	Donation	None (how long)	Income per month
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														

III. SHORT INTERNAL EXAMINATION

General examination
Body weight : ..... kg.
Height : ..... cm.
Respiration : ..... /minute
Pulse :
Frequency : ..... /minute
Regular/irregular : .....
Pulsus celer : .....
Bounding on palpation : .....
Pistol-shot sound on auscultation : .....
Blood pressure : .....
Face (puffy appearance) : .....
Neck :
Neck vein engorgement : .....
Increased jugular pulsation : .....
Extremities :
Atrophy of arm/leg muscles : .....
Oedema of medial side of tibia: .....
ankle: .....
lower leg : .....
Peripheral cyanosis : .....

Heart
Inspection : Ictus at intercostal space : .....
Enlarged : .....

Palpation : Ictus at intercostal space : .....
Percussion :
(The boundaries) .....
Auscultation :
Gallop rhythm : .....
Murmurs : .....
Others : .....

Lungs
Pleural effusion : .....
Rales on bases of the lungs : .....

Liver
Not palpable : .....
Enlarged : ..... cm, below the costal margin

Spleen : .....
Ascites : .....

IV. SHORT PSYCHIATRIC EXAMINATION

Intelligence : .....
Thought : .....
Orientation
Place : .....
Time : .....
Person : .....
Emotion & affect : .....
Psychomotor : .....
Delusion : .....
Hallucination : .....

V. SHORT NEUROLOGICAL EXAMINATION

Cranial nerves

Motor system

Walk on toes : .....
Walk on heels : .....
Squat test : .....

Leg

Tenderness of calf or thigh muscles : .....
Dorsal flexion of the great toe : .....
Plantar flexion of the great toe : .....
Dorsal flexion of the foot : .....
Plantar flexion of the foot : .....
Flexion of the lower leg : .....
Extension of the lower leg : .....
Flexion of the thigh : .....
Extension of the thigh : .....

Arm

Tenderness of the lower/upper arm : .....
Hand grip : .....
Flexion of the thumb : .....
Extension of the thumb : .....
Flexion of the hand : .....
Extension of the hand : .....
Flexion of the lower arm : .....
Extension of the lower arm : .....
Abduction of the upper arm : .....
Adduction of the upper arm : .....

Sensory system

Leg

Semmes-Weinstein test : .....
Glove-stocking sensation : .....
Vibration sense : .....
Pain sensation : .....
Position sense : .....
Temperature sense : .....

Arm

Semmes-Weinstein test : .....
Glove-stocking sensation : .....
Vibration sense : .....
Pain sensation : .....
Position sense : .....
Temperature sense : .....

Autonomic Nervous System

Profuse sweating : .....
Cold extremities : .....
Anorexia : .....

Reflexes

Knee jerk : .....
Ankle jerk : .....
Biceps tendon reflex : .....
Triceps tendon reflex : .....
Babinski : .....
Hoffmann Trömner : .....

GRADING OF MUSCLE STRENGTH AND WEAKNESS (MAYO CLINIC)
(Aronson et al.)(1971)

0 = normal
0 - 1 = Questionable weakness
- 1 = Slightest detectable weakness
-1,2 = Slight but not slightest weakness; loss of strength considerably less than 50%
- 2 = Moderate weakness; 50% strength
-2,3 = Between grades above and below (-2 and -3)
- 3 = Severe weakness but capable of moving extremity against gravity plus appreciable resistance made by examiner (75%)
-3 +g = Severe weakness; ability barely to move extremities through full range against gravity alone

-3 -g = Severe weakness; inability to move extremity through full range against gravity
-3,-4 = very severe weakness (minimal detectable contraction)
-4 = complete paralysis

VI. LABORATORY EXAMINATION

Haemoglobin : .....
Blood sedimentation rate : .....
Leukocyte : .....
Differential count : .....
Serum creatinine : .....
Blood ureum nitrogen : .....
Fasting blood sugar : .....
2 hours post prandial : .....
Serum glutamic-oxaloacetic transaminase .....
Serumglutamic-pyruvic transaminase : .....
Serum total protein : .....
Serum albumin : .....
Serum creatinine phosphokinase : .....
Blood thiamine : .....
Cerebrospinal fluid : .....

VII. SPECIAL EXAMINATION

ELECTROCARDIOGRAM :
Flattening or inversion of T-wave : .....
Sinus tachycardia : .....
Arrhythmia : .....
Others : .....

X-PHOTO OF THE CHEST :
Cardio-thoracic ratio : .....
Pulmonary vasculature : .....
Infiltrates : .....
Others : .....

Annex 3

NEUROPHYSIOLOGICAL EXAMINATION OF BERIBERI POLYNEUROPATHY

Name	:	Number of outpatient	
Sex (M/F)	:	clinic card	:
Present address	:	Date of admittance	:
Date of visit to		Number of inpatient	
the outpatient clinic	:	clinic card	:

PROCEDURE / DATE	Normal value
PERONEAL MOTOR	
Latency time	
ankle	3.77 ± 0.62 MSEC
knee	10.79 ± 1.06 MSEC
Amplitude	
ankle	5100 ± 2300 μV
knee	5100 ± 2000 μV
MCV	52.6 ± 3.8 M/SEC
POSTERIOR TIBIAL MOTOR	
Latency time	
ankle	3.86 ± 0.6 MSEC
knee	12.05 ± 1.5 MSEC
Amplitude	
ankle	5800 ± 1900 μV
knee	5100 ± 2200 μV
MCV	47.2 ± 3.6 M/SEC
MEDIAN MOTOR	
Latency time	
wrist	3.49 ± 0.34 MSEC
elbow	7.39 ± 0.69 MSEC
Amplitude	
wrist	5100 ± 3000 μV
elbow	5100 ± 2700 μV
MCV	57.7 ± 3.8 M/SEC
ULNAR MOTOR	
Latency time	
wrist	2.59 ± 0.39 MSEC
elbow	8.04 ± 0.76 MSEC
Amplitude	
wrist	5700 ± 2000 μV
elbow	5500 ± 1900 μV
MCV	58.7 ± 5.3 M/SEC
SENSORY NERVE (ORTHODROMIC)	
Sural nerve	
distal latency	2.08 ± 0.35 MSEC
amplitude	5.0 μV
Median nerve	
distal latency	2.84 ± 0.34 MSEC
amplitude	10.0 μV

Ulnar nerve
distal latency ..... 2.54 ± 0.29 MSEC
amplitude ..... 5.0 μ
H-REFLEX (M.soleus)
distal latency ..... 25.8 ± 1.8 MSEC
amplitude ..... 11238.1 ± 4097.6 μV

F-WAVE LATENCY
Posterior tibial nerve
ankle ..... 47.7 ± 5.0 MSEC
knee ..... 39.6 ± 4.4 MSEC
Median nerve
wrist ..... 26.6 ± 2.2 MSEC
elbow ..... 22.8 ± 1.9 MSEC
Ulnar nerve
wrist ..... 27.6 ± 2.2 MSEC
elbow ..... 23.1 ± 1.7 MSEC

MUSCLES
Ant.tib.
Normal .....
Positive sharp wave .....
Fibrillation .....
Decreased Compound
Muscle Action Potential .....
Others .....
Gastrocnemius
Normal .....
Positive sharp wave .....
Fibrillation .....
Decreased Compound
Muscle Action Potential .....
Others .....
Abd. poll.brevis
Normal .....
Positive sharp wave .....
Fibrillation .....
Decreased Compound
Muscle Action Potential .....
Others .....
Abductor digiti minimi
Normal .....
Positive sharp wave .....
Fibrillation .....
Decreased Compound
Muscle Action Potential .....
Others .....

CARDIAC BERIBERI SURVEY

Name	:	Domicile	
Family member no.	:	Rent a room	:
Sex (M/F)	:	Own house	:
Age	:	Dorm	:
Present address	:	Date of visit to the	
Place of birth	:	outpatient clinic	:
Job	:	Number of outpatient	
Income per month		clinic card	:
If unemployed :		Date of admittance	:
Job of your husband/		Number of inpatient	
wife/income	:	clinic card	:
Job of your father/		Interviewer	:
mother/income	:		

I.ANAMNESIS

1. Do you feel pins and needles or numbness of the fingers or toes or palm/plantar side of the foot? ..... Since when? Which is more severe the foot or the hand?.....
2. Do you feel paraesthesia when squatting?.....Since when? After how many minutes squatting do you feel the paraesthesia? .....
3. Do you feel paraesthesia when sitting on the floor with legs crossed?.. Since when? After how many minutes cross-legged do you feel the paraesthesia? .....
4. Do you suffer from cramps in the gastrocnemius muscles or feet, especially during sleep at night? .....
5. Do you suffer from glove-stocking sensation? .....
6. Have you ever had oedema of the feet, ankles or lower legs? Since when?.....
7. Do you suffer from unusual fatigue or malaise? .....
8. Forgetfulness ? Increased irritability ? Loss of interest in daily tasks or disorderly thinking? .....
9. Do you feel heavy or quickly fatigued or weak in the legs when running or doing a sport? .....
10. Do you suffer from shortness of breath when going upstairs or palpitation after walking? .....
11. Do you awake at night due to shortness of breath? .....
12. How many pillows do you use when sleeping to prevent shortness of breath? .....Do you suffer from orthopnea? .....
13. How many times do you urinate at night (nycturia)? .....
14. What is your hobby? Sprinter? Lifter? Others? .....
15. Are you an alcoholic? What kind of liquor do you drink? How many glasses do you drink a week? .....
16. Do you smoke ? Have you ever smoked marihuana? .....
17. Did you suffer from fever before the attack? Diabetes mellitus? Kidney disease? Morbus Hansen? Others? .....
18. What kind of traditional medicine do you often take? .....
    Do you take antacids? Are you in contact with insecticides? .....
19. How many times do you eat a day? .....
    Do you often consume instant noodles or soft drinks? .....
20. How many hours do you work or study a day? .....
    How many hours do you sleep a day? .....

II. SHORT NEUROLOGICAL EXAMINATION

Cranial nerves

Motor system

Walk on toes : .....
Walk on heels : .....
Leg
Tenderness of calf or thigh muscles : .....
Dorsal flexion of the great toe : .....
Plantar flexion of the great toe : .....
Dorsal flexion of the foot : .....
Plantar flexion of the foot : .....
Flexion of the lower leg : .....
Extension of the lower leg : .....
Flexion of the thigh : .....
Extension of the thigh : .....

Arm
Tenderness of the lower/upper arm : .....
Hand grip : .....
Flexion of the thumb : .....
Extension of the thumb : .....
Flexion of the hand : .....
Extension of the hand : .....
Flexion of the lower arm : .....
Extension of the lower arm : .....
Abduction of the upper arm : .....
Adduction of the upper arm : .....

Sensory system

Leg
Semmes-Weinstein test : .....
Glove-stocking sensation : .....
Vibration sense : .....
Pain sensation : .....
Position sense : .....
Temperature sense : .....

Arm
Semmes-Weinstein test : .....
Glove-stocking sensation : .....
Vibration sense : .....
Pain sensation : .....
Position sense : .....
Temperature sense : .....

Autonomic Nervous System

Profuse sweating : .....
Cold extremities : .....
Anorexia : .....

Reflexes

Knee jerk : .....
Ankle jerk : .....
Biceps tendon reflex : .....
Triceps tendon reflex : .....
Babinski : .....
Hoffmann Tromner : .....

III. SHORT INTERNAL EXAMINATION

General examination
Body weight : ..... kg.
Height : ..... cm.
Respiration : ..... /minute
Pulse :
Frequency : ..... /minute
Regular/irregular : .....
Pulsus celer : .....
Bounding on palpation : .....
Pistol-shot sound on auscultation : .....
Blood pressure : .....
Face (puffy appearance) : .....
Neck :
Neck vein engorgement : .....
Increased jugular pulsation : .....
Extremities :
Atrophy of arm/leg muscles : .....
Oedema of medial side of tibia: .....
ankle: .....
lower leg : .....
Peripheral cyanosis : .....

Heart
Inspection : Ictus at intercostal space : .....
Enlarged : .....

Palpation : Ictus at intercostal space : .....
Percussion :
(The boundaries) .....
Auscultation :
Gallop rhythm : .....
Murmurs : .....
Others : .....

Lungs
Pleural effusion : .....
Rales on bases of the lungs : .....

Liver
Not palpable : .....
Enlarged : ..... cm, below the costal margin

Spleen : .....
Ascites : .....

IV. SPECIAL EXAMINATION

ELECTROCARDIOGRAM :
Flattening or inversion of T-wave : .....
Sinus tachycardia : .....
Arrhythmia : .....

HEART CATHETERIZATION :
Saturation & pressure in the atrium/
right ventricle : .....
Saturation & pressure in the pulmonary
artery, PCWP* : .....
Cardiac output : .....
Cardiac index : .....
Arteriovenous oxygen ratio : .....
Pulmonary vascular resistance (PVR) :.....

ECHOCARDIOGRAPHY :

Dimension of the ventricles of the heart : ..... cm
Movements of the heart walls : .....
Heart function .....
Thrombus .....
Pericardial effusion .....
Cardiac output .....

THORAX PLAIN X-PHOTO

Cardiac thoracic ratio : .....
Pleural effusion : .....
Pulmonary congestion : .....
Pulmonary vasculature : .....

V. BIOCHEMICAL EXAMINATION

Haemoglobin : .....
Blood sedimentation rate : .....
Leukocyte : .....
Differential count : .....
Haematocrit : .....
Serum creatinine : .....
Fasting blood sugar ; .....
2 hours post prandial : .....
Blood ureum nitrogen : .....
Thymol turbidity test : .....
Serum glutamic-oxaloacetic transaminase : .....
Serum glutamic-pyruvic transaminase : .....
Serum total protein : .....
Serum albumin : .....
Serum globulin : .....
Blood thiamine : .....
Serum sodium : .....
Serum potassium : .....
Serum chlor : .....
Serum Lactic Acid : .....
Blood gas analysis : .....
Cerebrospinal fluid : .....
(if necessary)

VI. FOLLOW UP

	DATE
Body weight	:
Blood pressure	:
Pulse rate during sound sleep	:
Diuresis (ml/24 hours)	:
Electrocardiogram	:
Thorax photo	
Cardiothoracic ratio	:
Pleural effusion	:
Pulmonary congestion	:
Pulmonary vasculature	:
Blood gas analysis	
pH	:
pCo2	:
pO2	:
HCO3	:
Blood thiamine	:
Echocardiography	
Dimension of Right Atrium	:
Dimension of Right Ventricle	:
Dimension of Left Atrium	:
Dimension of Left Ventricle	:
Wall movements	:
Heart function	:
Cardiac output	:
Cardiac index	:
Exercise stress test	
Functional capacity	:
Reason at termination	:
Arrhythmia	:
Others	:
Heart catheterization	
Pressure & saturation of:	
Right Atrium	:
Right Ventricle	:
Mean pulmonary artery (MPA)	:
PCWP*	:
Arterio-venous O2 difference	:
Cardiac output	:
Cardiac index	:
Lung Function	
VC (vital capacity)	:
FEV1**	:
Maximal breathing capacity (MBC)	:

Note : * PCWP = pulmonary capillary wedge pressure
** FEV1 = forced expiratory volume at one second

Annex 5

PROTOCOL EXPERIMENTALLY INDUCED BERIBERI POLYNEUROPATHY IN CHICKENS

Code number	:	Amount of rice (g)	:
Colour of the feathers	:	How cooked	:
Age (months)	:	Kind of vegetable	:
Sex	:	Amount of vegetable	:
Sort of rice (distributed white rice or red rice)	:	Date of experiment	:

		WEEK											
		1	2	3	4	5	6	7	8	9	10	11	12
GENERAL EXAMINATION													
Body weight	:												
Colour of face	:												
Crow	:												
Cackle	:												
Flapping wings	:												
Scratching	:												
Walking along a roost	:												
Appetite	:												
Colour of stool	:												
INTERNAL & NEUROLOGICAL EXAMINATION													
Breathing													
Normal (20-30/min.) (0)	:												
< 20-30/min. (-½)	:												
Dyspnea (-1)	:												
Emptying of bowel (crop)													
Good (0)	:												
Delayed (-1)	:												
Consciousness													
Alert (0)	:												
Apathy (-½)	:												
Sopor (-1)	:												
Sensory function													
Flexion to pain (0)	:												
Minimal reaction (-½)	:												
No reaction (-1)	:												
Motor function													
Gait													
normal (0)	:												
ataxic (-½)	:												
none (-1)	:												
Posture													
normal (0)	:												
oblique (-½)	:												
none (-1)	:												
Sitting													
normal (0)	:												
not upright (-½)	:												
none (-1)	:												
Running													
normal (0)	:												
paretic (-½)	:												
none (-1)	:												

Pick up food		
normal	(0)	:
incorrect	(-½)	:
none	(-1)	:
Position of head/neck		
normal	(0)	:
curled	(-½)	:
none	(-1)	:

Total score

NEUROPHYSIOLOGICAL EXAMINATION

NERVE/F-WAVE/SSEP/MUSCLE	WEEK 1 3 5 7 9 11 12	NORMAL VALUE
PERONEAL MOTOR		
LATENCY TIME		
Ankle		2.2 ± 0.3 MSEC
Knee		4.42 ± 0.56 MSEC
AMPLITUDE		
Ankle		1500 ± 428.4 μV
Knee		1530 ± 548.33 μV
MCV		45.3 ± 5.2 M/SEC
SCIATIC MOTOR		
LATENCY TIME		
Sciatic notch		5.46 ± 0.6 MSEC
AMPLITUDE		
Sciatic notch		1505 ± 432.08 μV
MCV		63.71 ± 14.2 M/SEC
PERONEAL SENSORY		
Distal latency		1.35 ± 0.19 MSEC
Amplitude		6.5 ± 3.34 μV
F-WAVE		
DISTAL LATENCY		
Ankle		13.06 ± 1.56 MSEC
Knee		12.22 ± 1.53 MSEC
AMPLITUDE		
Ankle		295 ± 260.8 μV
Knee		380 ± 407.7 μV
PERONEAL SSEP		
P1		18.93 ± 1.8 MSEC
N1		28.38 ± 1.8 MSEC
GASTROCNEMIUS MUSCLE		
AT REST		
Normal		
Positive spikes		
Fibrillation		
Others		
MINIMAL CONTRACTION		
PERONEAL MUSCLE		
AT REST		
Normal		
Positive spikes		
Fibrillation		
Others		
MINIMAL CONTRACTION		

FOLLOW-UP:

	D A T E	NORMAL VALUE
BIOCHEMICAL EXAMINATION		
Haemoglobin	.....	10.11 ± 0.53 G%
Serum albumin	.....	1.53 ± 0.30 G%
NEUROMORPHOLOGICAL EXAMINATION		

Annex 6

FOOD PATTERN SURVEY
DEPARTMENT OF NUTRITION, DR. SOETOMO HOSPITAL,
SURABAYA, INDONESIA

Name	:	Date of admittance	:
Sex (M/F)	:	Number of inpatient	
Age	:	clinic card	:
Present address	:	Medications	:
Occupation	:	Date of interview	:
Education	:	Interviewer	:
Date of visit to the		Height (cm)	:
outpatient clinic	:	Weight (kg)	:
Number of outpatient			
clinic card	:		

1. FREQUENCY OF CONSUMPTION

TYPE OF FOOD	HOW MANY TIMES A DAY	1X/ DAY	4-6X/ WEEK	3X/ WEEK	1-2X/ WEEK	1X/ WEEK	NEVER
> 0.5 MG THIAMINE/100 G SUBSTANCE							
LEAN PORK							
DUCK'S EGG YOLK							
PIG'S KIDNEY							
RICE BRAN							
MUNG BEANS							
COW PEAS							
SOY MILK POWDER							
0.1 MG - 0.5 MG THIAMINE/100 G SUBSTANCE							
LEAN COW'S MEAT							
CHICKEN EGG							
STEAMED SALTED DECAPTERUS KURRA (PINDANG)							
STOLEPHORUS SPECIES (TERI)							
MILK							
FERMENTED SOYBEAN CAKE (TEMPE)							
PEANUTS							
MILLED RICE							
GLUTINOUS RICE							
CORN							
POTATOES							
WHITE BREAD							
COLOCASIA ESCULENTA (TALAS)							
RICE FLOUR							
LEAFY VEGETABLES							
MUNG BEAN SPROUTS							
< 0.1 MG THIAMINE/100 G SUBSTANCE							
CHICKEN							
MILK FISH							
SALTED FISH							
SOYBEAN CURD							
CASSAVA							
YAM							
CRACKERS							
VEGETABLES							
FRUIT							

2. HOW MANY TIMES A DAY DO YOU EAT?
   ONCE : .....
   TWICE : .....
   THREE TIMES : .....

3. SERVINGS PER DAY

	GRAMS	HOUSEHOLD MEASUREMENTS
BREAKFAST		
RICE	.....	
MEAT/EGG/FISH	.....	
TEMPE/BEAN CURD	.....	
VEGETABLES	.....	
FRUIT	.....	
10.00 A.M.		
MILK	.....	
MUNG BEANS	.....	
SNACK	.....	
OTHERS	.....	
LUNCH		
RICE	.....	
MEAT/EGG/FISH	.....	
TEMPE/BEAN CURD	.....	
VEGETABLES	.....	
FRUIT	.....	
16.00 P.M.		
MILK	.....	
MUNG BEAN	.....	
OTHERS	.....	
DINNER		
RICE	.....	
MEAT/EGG/FISH	.....	
TEMPE/BEAN CURD	.....	
VEGETABLES	.....	
FRUITS	.....	

4. HOW DO YOU COOK THE RICE ?
   STEAMED (KUKUS) : .....
   COOKED (LIWET) : .....
   COOKED & STEAMED (KRONCONG) : ...
   PORRIDGE : .....
   COOKED FOR A LONG TIME : .....
   & PACKED WITH BANANA LEAVES
   (LONTONG)

5. WASHING THE RICE ?
   ONCE : .....
   TWICE : .....
   THREE TIMES : .....
   OTHERS : .....

6. DO YOU COOK THE RICE YOURSELF ?

7. IF YOU DO NOT COOK ,
   DO YOU BUY IT ? .....
   CATERING ? .....
   EAT AT YOUR OFFICE ? .....

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CURRICULUM VITAE

The author of this thesis was born in Sumenep, Madura, Indonesia on March 30, 1931. He graduated from high school in Surabaya in 1952. In the same year he started his medical study at the Faculty of Medicine, Airlangga University, Surabaya. After finishing his medical study in 1961 he worked as a residence in the Department of Neurology and Psychiatry, Faculty of Medicine, Airlangga University, Surabaya, under the guidance of Professor H.R.M. Soejoenoes MD. In 1966 he was registered as a neurologist and psychiatrist. In 1973 he was appointed as a staffmember of the Department of Neurology, of the same University in Surabaya.

In 1982-1983 he studied neurophysiology at the Department of Clinical Neurophysiology, Institute of Neurology, St.Radboud University Hospital, Nijmegen, The Netherlands (head: Professor S.L.H. Notermans MD PhD). He also worked for one year at the Neuromorphological Laboratory of the University, for an upgrading course (head: H.H.J. Jaspar, MD).

In 1983 he received training in classical acupuncture from The Dutch Physicians' Association of Acupuncture (Nederlandse Artsen Acupunctuur Vereniging) at Santpoort, The Netherlands.

He interested in beriberi neuropathy when he noticed an increasing trend towards neuropathy in the year 1981 especially in low income groups, which could not be attributed to the common causes such as diabetes mellitus, uremia, leprosy, Guillain Barré syndrome, or toxic neuropathy.

He became a member of the Indonesian Neurological Association in 1973, the Indonesian Society for Clinical Neurophysiology in 1983, the Indonesian Society against Epilepsy in 1986, the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) in 1988, the Indonesian board of Neurological Research Project in 1988, the Indonesian Society for Cerebro-vascular Disorders in 1989.

In 1984 he was appointed as Clinical Neurophysiologist of the Department of Neurology of the Dr.Soetomo Hospital, Surabaya, and since 1987 he is one of the editorial board of the Indonesian Journal of Neurology (Aksona) in Surabaya

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PROPOSITIONS

belonging to the thesis

BERIBERI IN LOW INCOME GROUPS

A clinical and experimental study
in Surabaya and surroundings

Nijmegen, December 13, 1991

DJOENAIDI WIDJAJA

1

It has never been reported that beriberi exists on such a great scale in Indonesia as we reported in this thesis and it is almost certain that the disease is frequently underdiagnosed.
This thesis

2

A tingling sensation in the distal ends of the extremities, easy fatigability, and muscle cramps are the early symptoms of beriberi polyneuropathy.
This thesis

3

The "walk on heels" test is more reliable than the "squat" test in diagnosing beriberi polyneuropathy.
This thesis

4

Symmetrical reduction of the distal amplitude of the peroneal motor nerve, reduced amplitude of the H-reflexes, and abnormal electromyography of the distal leg muscles are the early neurophysiological signs of beriberi polyneuropathy.
This thesis

5

Small daily doses of thiamine do not prevent patients from developing thiamine deficiency while on intravenous hyperalimentation regimens.
This thesis

6

Wernicke's encephalopathy should be considered in patients of low income groups with unexplained confusion, obtundation, or sudden coma.
Harper C, Gold J, Rodriguez M, Perdices M. J Neurol Neurosurg Psychiatry 1989; 52: 282-285

7

One should bear in mind beriberi heart disease in young patients of low income groups with acute heart failure of obscure origin.
This thesis

8

The treatment of acute idiopathic inflammatory polyradiculoneuropathy or the Guillain-Barré syndrome by fresh frozen plasma exchange is recommended in countries with financial constraints and poor facilities.
DeSilva HJ, Gamage R, Herath HKN et al. Postgr Med J 1987; 63: 1079-1081

9

Lacunar infarctions which have been thought to be associated with hypertensive arteriolar sclerosis of small perforating vessels, were sometimes caused by severe, ipsilateral internal carotid artery occlusion.
Waterston JA, Brown MM, Butler P and Swash M. Arch Neurol 1990; 47: 953-957

10

Electrophysiologic tests may be the most sensitive indicators of asymptomatic carriers of HIV infections.
Koralnik IJ, Beaumanoir A, Häusler R et al. N Engl J Med 1990; 323: 864-870

11

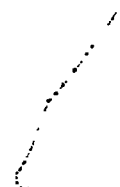
A growing body of pathological, clinical and neurophysiological evidence suggests that sensory pathways may be involved in motor neuron disease.
Subramaniam JS and Yiannikas C. Arch Neurol 1990; 47: 989-994

12

Diagnoses are missed not because of lack of knowledge on the part of the examiner but rather because of lack of examination.
Sir William Osler

13

The growing number of tourists from the Western World visiting developing countries is a mixed blessing; it gives insight into the ways of the Western World, but at the same time it may have a negative impact on a country's culture, and it may entail the import of diseases.



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