MEDICAL GRAND ROUNDS

MAY 30, 1974

WERNICKE'S ENCEPHALOPATHY

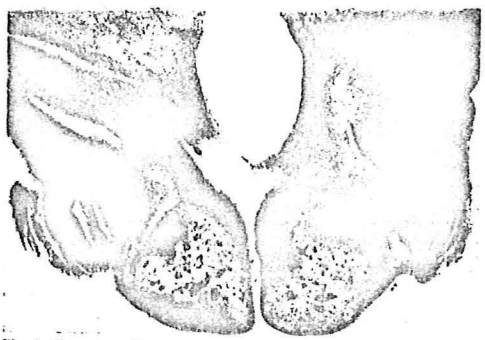


Fig. 1.—Frozen section through mammillary bodies showing dilated vessels and hæmorrhages, and a smaller lesion in the wall of the 3rd ventricle. (Lepehne Pickworth, × 4½.)

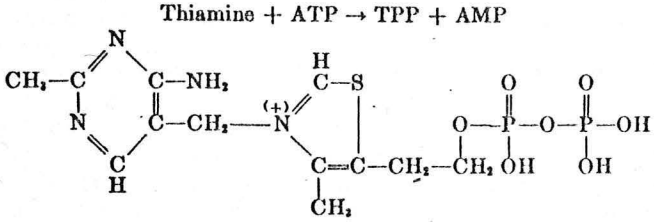
RELATED DISORDERS

AND

FACTORS ASSOCIATED WITH THE

PRODUCTION OF THIAMINE DEFICIENCY

Thiamine + ATP → TPP + AMP



Thiamine pyrophosphate (TPP)

Leonard L. Madison, M.D.

TABLE I

THIAMINE - ROLES IN METABOLISM

I. FORMS OF THIAMINE IN THE BODY (ref 1-3)

A. THIAMINE DIPHOSPHATE (PYROPHOSPHATE) - TDP
Synthesized from thiamine and ATP
Enymatic reaction requires Mg^{++}
Thiamine + ATP $\xrightarrow{Mg^{++}}$ TDP + AMP
Constitutes 80% of Body Thiamine

B. THIAMINE TRIPHOSPHATE - TTP (ref 74-77)
Synthesized from TDP and ATP by the enzyme TDP-ATP phosphoryltransferase
TDP + ATP $\longrightarrow$ TTP + ADP
Constitutes 10% of Body Thiamine

C. THIAMINE MONOPHOSPHATE (TMP) $>$ 10% Body Thiamine

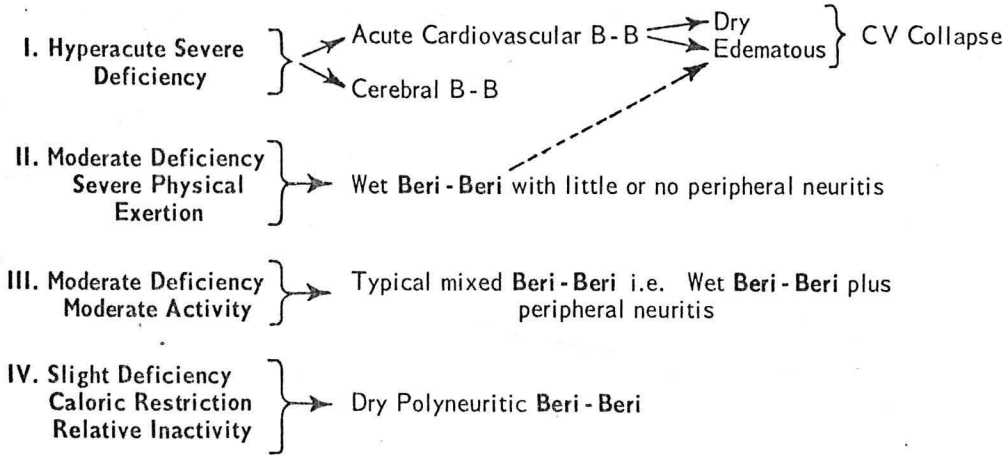
D. FREE THIAMINE

II. ACTIONS OF THIAMINE (ref 1-3)

A. THIAMINE DIPHOSPHATE - "COCARBOXYLASE"
1. Glycolytic Pathway
Oxidative-decarboxylation of pyruvate to Acetyl CoA
2. Citric Acid Cycle
Oxidative-decarboxylation of α-ketoglutarate to succinate
3. Pentose-Phosphate Pathway
Two transketolase reactions with the transfer of 2 carbon unit from Xylulose-5-P
a. To Ribose-5-P form sedoheptulose-7-P and glyceraldehyde-3-P
b. To Erythrose-4-P to form Fructose-6-P and glyceraldehyde-3-P

B. OTHER FORMS OF THIAMINE (ref 74-77)
1. TTP is the neurophysiologically active form of thiamine (Cooper et al.)
2. TTP important in the binding of TDP to its apoenzyme (Yusa & Maruo)
3. Evidence in support of a coenzyme-independent role of thiamine in the nervous tissue
a. Inconsistencies in the correlation between neurological signs in thiamine deficiency and activity of TPP-dependent enzymes in nervous tissue
b. Electrophysiological effects of pyrithiamine, an antimetabolite of thiamine, are due to displacement of thiamine from the nerve, rather than to enzyme inhibition
c. Thiamine is localized in nerve membranes, as opposed to axoplasm
d. Both electrical stimulation and neuroactive drugs release thiamine from a variety of intact nerve preparations. Neuroactive drugs also specifically release the vitamin from nerve membrane fractions
e. As nerve membranes are purified from a brain homogenate, the percentage of the thiamine triphosphate (TTP) form of the vitamin increases
f. Thiamine restores the action potential in an ultra-violet irradiated nerve

TYPES OF BERI-BERI AND PREDISPOSING FACTORS



CLINICAL PICTURE OF CEREBRAL BERI-BERI

Signs and Symptoms in Order of Appearance

1. **Vomiting** - Persistent, effortless
2. **Nystagmus** - Starts few days after vomiting
   Horizontal more frequent than vertical
   At times elicited only by lateral gaze
3. **Palsy of External Rect.** - Unilateral or bilateral
   Nystagmus decreases with appearance of ocular palsy
4. **Progressive Mental Deterioration** -
   Loss of interest - Present and past
   Dull apathy → Confabulation → Disorientation →
   Hallucinations → Coma → Death
5. **Fever** - Unexplained - probably central
6. **Ataxia** - Frequently absent - Ataxia of gait
   Seldom seen in individual movements of arms or legs

TABLE II

NEUROLOGICAL CONSEQUENCES OF THIAMINE DEFICIENCY (ref 4-25)

I. ACCEPTED (4-10)

A. PERIPHERAL NEUROPATHY

B. WERNICKE'S ENCEPHALOPATHY

C. KORSAKOFF'S PSYCHOSIS

II. PROBABLY RELATED TO THIAMINE DEFICIENCY (10,11)

A. CEREBELLAR DEGENERATION

B. AMBYLOPIA

C. MARCHIAFAVA-BIGNAMI DISEASE

D. CENTRAL PONTINE MYELINOLYSIS

III. POSSIBLE DEPENDENCY ON INCREASED REQUIREMENTS FOR THIAMINE (74-87)

A. LEIGH'S DISEASE - SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY (74-81)

B. ONDINE'S CURSE - FAILURE OF AUTOMATIC CONTROL OF VENTILATION (82,83)

IV. GENETIC THIAMINE-DEPENDENT STATES (24,25)

Table 3. The Vitamin-responsive Inborn Errors of Metabolism (Hereditary Vitamin Dependencies)

Vitamin	Dose for Treatment (Per Day)	Disease	Apoenzyme Affected Proven or Presumed(?)	Comments on Apparent Mechanism of Vitamin Responsiveness	References
Thiamine (B_1)	20 mg	Megaloblastic anemia	Unknown	Two reports; mechanism unknown	47
	5–20 mg	Intermittent cerebellar ataxia	Pyruvate dehydrogenase (?)	Several forms probably. Mechanism of response to massive doses unknown; response equivocal	48, 49
	5–20 mg	Lactic acidosis	Pyruvate carboxylase	Probable "shunt" mechanism via pyruvate dehydrogenase	50
	5–20 mg	Branched-chain aminoacidopathy (MSUD variant)	Branched-chain keto acid dehydrogenase (decarboxylase component)	Clinically, "mild" form. Residual enzyme activity (10%–15% normal). Thiamine may increase amount of mutant enzyme	51

CASE I [redacted] - admitted [redacted] Died [redacted]

This 52 year old chronic alcoholic woman was brought to the hospital in a confused state. About 2 weeks prior to admission she developed post prandial nausea and vomiting which lasted several days. About this time her son noted that she was displaying mental changes, some confusion and loss of memory. Following this, weakness of the legs, unsteady gait, anorexia and progressive mental changes were noted. Six days PTA she became febrile, and more confused. She was placed on oral antibiotics which were given until the time of admission without improvement in her clinical condition.

She had been a heavy drinker for 16 years, consuming about 1 pint of of whiskey or a bottle of wine per day in addition to a large amount of beer.

Px on admission revealed an acutely ill woman, confused, lethargic, disoriented who was dehydrated and febrile. B.P. 110/60 P.92 R.22 T.104. No spider angiomata were seen but the liver was felt 2F↓ CM. The heart and lungs were normal. Neurological examination revealed diminished DTR's in the arms and absent DTR's in the legs. Nystagmus and EOM paralysis were not found. Initial chemistries revealed CO_2 21 mEq/L, Cl 106 mEq/L bilirubin 3.2 mg%.

Thiamine deficiency was not suspected on admission. The apparent dehydration was treated with 1L of NaCl and 4L of 5% glucose. No vitamins were given. Shortly thereafter the patients blood pressure fell from 110/80 to 80/50. Levophed was begun and the patient given another 4L of glucose. The collapse worsened and did not respond to increasing amounts of levophed and hydrocortisone. By 7:30 p.m. on [redacted] she was edematous and in profound collapse without obtainable blood pressure. She died shortly thereafter.

Post mortem examination revealed the classical findings of Wernicke's Encephalopathy, focal necrosis of the heart muscle and portal cirrhosis.

CASE II [redacted] Admitted [redacted]/72

This was the third [redacted] admission of this 51 year old man who was previously admitted in [redacted] 1962 and [redacted] 1966 for Wernicke's Encephalopathy, Korsakoff's Psychosis and Chronic Alcoholism. Prior to this admission, the patient had been drinking heavily for a long time. About a week PTA he developed anorexia with occasional vomiting. This was followed by increasing confusion. Three days PTA he became bedridden because of ataxia and weakness. At this time he stopped drinking. Because of this sequence of events he was brought to the emergency room and admitted. Initial examination revealed bilateral laterol recti muscle paralysis, dysconjugate gaze but no nystagmus. He was oriented to person only, showed poor short term memory and confabulated freely. There were also apparent auditory hallucinations and misinterpretation of his surroundings. T.P.R. were normal. The remainder of the physical was none contributory. Initial lab - T.P. 7.9, alb 3.6, Ca 9.9, Gluc. 110, BUN 11, Bili 1.1, SGOT 149, Hgb 13, Hct 40, MCV 107. Skull and chest X-rays negative.

The patient was given large amounts of thiamine folate and multivitamins. By the next morning his EOM were normal and mild nystagmus was noted. This disappeared by the next day. Korsakoff's Psychosis improved slowly but at the time of discharge, while improved, he was far from normal according to his wife.

Page Missing in Original Volume

GLOBAL CONFUSIONAL STATE

A Quiet, Hypokinetic Delirium - Composed of:

1. General Fatigue and Apathy
2. Impairment of Awareness and Responsiveness
3. Disorientation and Confusion
4. Inattention and Failure to Concentrate
5. Derangements of Perception and Memory

Except for Defect in Memory - Favorable Response to B_1

KORSAKOFF'S PSYCHOSIS

1. In 80% of cases - As symptoms of Global Confusional State subsided in days to week, Korsakoff's stood out in pure form

2. In 20% Korsakoff's Psychosis was recognized at onset

3. Only 9 of 245 cases of Korsakoff's Psychosis (3.7%) were not preceded by Wernicke's Encephalopathy

4. Characterized by

   a. Retrograde Amnesia - Inability to recall information acquired months to years before onset of illness

   b. Anterograde Amnesia - Impaired ability to acquire new information i.e. to learn or form new memories

   c. Confabulation - Neither consistently present nor essential for the diagnosis

   d. Usually alert, responsive and show no serious defects in social behavior

COURSE OF WERNICKE'S ENCEPHALOPATHY

MORTALITY - 17% DIED DURING ACUTE ILLNESS - AV. 8 DAYS (1-21)

MODE OF RECOVERY

EYE CHANGES

6th NERVE PALSY - Corrected In All
1/3 in 6 Hrs 1/3 in 7-24 Hrs 1/3 in 1-4 Days

HORIZONTAL GAZE PALSY - Complete Recovery

HORIZONTAL NYSTAGMUS - 40% Complete Recovery

ATAXIA

38% Complete Recovery
35% Incomplete Recovery
27% No Significant Improvement

MENTAL CHANGES

GLOBAL CONFUSIONAL STATE - Complete Recovery Unless Followed By Korsakoff's Psychosis

84% of WERNICKE'S Developed KORSAKOFF'S
Complete Recovery in 21%
Moderate Improvement in 25%
No Significant Improvement in 54%

SYMPTOMS AND SIGNS IN WERNICKE'S ENCEPHALOPATHY
(From DeWardener and Lennox - Ref #4)

SYMPTOMS

	No. of cases
Loss of appetite	46 (88%)
Eye symptoms:	33 (63%)
Wavering of fields of vision on looking to the side	24 (46%)
Diplopia	23 (44%)
Photophobia	3 (6%)
Nausea and vomiting	31 (57%)
Insomnia	20 (38%)
Giddiness	11 (21%)

SIGNS

(*a*) The *eye changes* can be classified as follows:

	No. of cases
Nystagmus	52 (100%)
External rectus fatigue and paralysis	14 (26%)
Complete disconjugate wandering	4 (8%)
Loss of visual acuity	2 (4%)
Papilloedema	2 (4%)
Pupil abnormalities	2 (4%)
Ptosis	1 (2%)
Complete ophthalmoplegia	1 (2%)
Retinal haemorrhages	1 (2%)

(*b*) *Mental changes* can be classified as follows:

	No. of cases
Emotional changes:	35 (67%)
Apprehension	17 (32%)
Apathy	17 (32%)
Excitement	7 (13%)
Memory loss for recent events	32 (61%)
Disorientation	24 (46%)
Confabulation and hallucinations	13 (25%)
Convulsions	1 (2%)
Sudden onset of advanced mental signs as first evidence of cerebral beriberi	10 (19%)

FINDING IN WERNICKE'S ENCEPHALOPATHY.
(From Victor, Adams and Collins - Ref 9)

Mental and behavioral abnormalities in 229 cases of the Wernicke-Korsakoff syndrome at the time of the initial examination

	Number	Per cent
Stupor	9	4
Coma	2	1
Alcohol abstinence syndrome*	36	16
Global confusional state	128	56
*Disorder of memory	131	57
No mental abnormality	23	10

Incidence of ocular abnormalities in 232 cases of the Wernicke-Korsakoff syndrome

Sign	No. of Cases		Per cent
Nystagmus		198 (65)*	85
Lateral Rectus Palsy, Bilateral		125 (7)	54
Complete	38 (5)		16
Partial	87 (2)		38
Conjugate Gaze Palsy		102 (6)	44
Pupillary Abnormality		43	19
Retinal Hemorrhages		6	3
Ptosis		8	3
Bilateral	6		3
Unilateral	2		<1
Central or Cecocentral Scotomata		6	3
No Ocular Abnormality		9	4

Incidence of ataxia in the Wernicke-Korsakoff syndrome

Abnormality	Incidence	Per cent
Ataxia of Gait	N = 188*	
Mild	67	36
Moderate	56	30
Severe	40	21
Normal	25	13
Ataxia of Legs	N = 188*	
Mild	28	15
Moderate	7	4
Severe	3	2
Normal	150	80
Ataxia of Arms	N = 191*	
Mild	15	8
Moderate	5	3
Severe	2	1
Normal	169	88
Ataxia of Speech	N = 180*	
Abnormal	15	8
Normal	165	92

Time of onset of improvement of the abnormalities in the Wernicke-Korsakoff syndrome* (expressed as per cent of cases in which adequate follow-up data were available)

Abnormality	Time After Institution of Treatment			
	1-24 hours	2-7 days	2-4 weeks	> 1 month
6th Nerve Palsy (N = 52)	62	38		
Gaze Palsy				
Horizontal (N = 45)	62	38		
Vertical (N = 26)	50	31	19	
Nystagmus				
Horizontal (N = 20)	15	40	40	5
Vertical (N = 28)	25	54	21	
Ataxia (N = 26)		58	35	7
Global Confusion (N = 48)	15	46	33	6
Korsakoff's Psychosis (N = 22)	0	9	27	64

FACTORS ASSOCIATED WITH THE PRODUCTION OF THIAMINE DEFICIENCY STATES

I. INADEQUATE INTAKE OF THIAMINE IN THE DIET

A. REVIEW OF NORMAL REQUIREMENTS (ref 24, 27-35)
B. FACTORS INCREASING REQUIREMENTS
   1. Fever - Infections (33)
   2. Hyperthyroidism (33)
   3. Exercise (33)
   4. Pregnancy - Lactation (33)
   5. High CHO Diet (21)
   6. Losses From Body
      a. Diuretics (29)
      b. Hemodialysis (22)
      c. Peritoneal Dialysis (23)
      d. Diarrheal States (43)
      e. Starvation - complete (35)

II. DEFECTIVE INTESTINAL ABSORPTION (ref 36-47)

A. REVIEW OF NORMAL ABSORPTION (ref 36-39)
B. MALABSORPTION STATES (38)
C. ACHLORHYDRIA AND ANTACID INGESTION (45)
D. EFFECTS OF ALCOHOL (40-42)
E. EFFECTS OF LIVER DISEASE (40-42)
F. EFFECTS OF FOLATE DEPLETION (46)

III. DEFECTIVE UTILIZATION - FAULTY HOLOENZYME FORMATION OR ACTION (ref 47-52)

A. LIVER DISEASE (47-52)
B. MAGNESIUM DEFICIENCY (51a)

IV. DESTRUCTION OF THIAMINE IN THE G.I. TRACT (53-73)

A. ROLE OF BACTERIAL SYNTHESIS IN DIETARY REQUIREMENTS (53-57)
B. BACTERIAL DESTRUCTION - "THIAMINASE DISEASE" OF JAPANESE (58-60)
C. THIAMINASE INGESTION - LESSONS FROM ANIMAL DISEASES
   CHASTEK'S PARALYSIS OF FOXES, CATS AND HORSES (61-73)
   (The Saga of the Silver Fox)
D. THE ENIGMA OF THIAMINE DEFICIENCY IN RUMINANTS

V. VITAMIN DEPENDENT GENETIC STATES (VITAMIN RESPONSIVE INBORN ERRORS OF METABOLISM) - REQUIRE CONTINUOUS PHARMACOLOGICAL DOSES OF THIAMINE (24,25)

A. THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA
B. THIAMINE RESPONSIVE INTERMITTENT CEREBELLAR ATAXIA
C. THIAMINE RESPONSIVE LACTIC ACIDOSIS
D. THIAMINE RESPONSIVE BRANCHED-CHAIN AMINOACIDURIA

VI. POSSIBLE VITAMIN DEPENDENT STATES ASSOCIATED WITH AN INHIBITOR OF THIAMINE PYROPHOSPHATE-ADENOSINE TRIPHOSPHATE PHOSPHORYL TRANSFERASE IN URINE AND BLOOD - REQUIRES PHARMACOLOGICAL DOSES OF THIAMINE (74-87)

A. LEIGH'S DISEASE - SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY (74-81)
B. ONDINE'S CURSE - FAILURE OF AUTOMATIC CONTROL OF RESPIRATION (81-87)

I. INADEQUATE INTAKE OF THIAMINE IN THE DIET

A. REVIEW OF NORMAL REQUIREMENTS

1. VITAMIN DEFICIENCY STATES - since vitamins are essential precursors of coenzymes, a deficient supply eventually affects all functions dependent on the precursor form.

   a. Leads to a broad spectrum of biochemical abnormalities
   b. Usually responds to replacement at the Recommended Daily Allowance (RDA)
   c. Dietary deficiency more or less obvious

2. VITAMIN-RESPONSIVE INBORN ERRORS OF METABOLISM (Ref 24, 28)

   a. Inherited disorder
   b. Involves a specific biochemical abnormality
   c. Responds only to pharmacological doses of the vitamin (10-1000X RDA)
   d. Lifelong specific requirement for pharmacological doses
   e. Augmented doses do not produce toxicity it might in a non-dependent person

3. DAILY REQUIREMENT FOR THIAMINE (Ref 27-35, 24)

   Minimal 0.33 mg/1000 kcal mixed diet
   RDA 0.54-0.66 mg/1000 kcal mixed diet
   Needs decreased by high fat intake
   Needs increased by high CHO intake - Minimal needs greater than 0.5 mg/1000 non-fat kcal
   Body Stores - Meager - between 25-30 mg

B. FACTORS INCREASING REQUIREMENTS

1. FEVER - INFECTIONS (33)

2. HYPERTHYROIDISM (33)

3. EXERCISE (33)

4. PREGNANCY - LACTATION (33)

5. HIGH CHO DIET (21)

6. LOSSES FROM BODY

   a. Diuretics (29)
   b. Hemodialysis (22)
   c. Peritoneal Dialysis (23)
   d. Diarrheal States (43)
   e. Starvation - complete (35)

II. DEFECTIVE INTESTINAL ABSORPTION OF THIAMINE

A. REVIEW OF NORMAL ABSORPTION (Ref 36-38)

1. Low doses of thiamine are absorbed in vivo in the small intestine by an active process (36)

2. Large doses of thiamine block the active process and are obsorbed by passive diffusion (36)

3. Duodenum and upper small intestine are the sites of maximum absorption in rats (37) and man (38)

4. A greater proportion of a small dose is absorbed than of a large dose (38)

Table II. Seventy-two hour urinary excretion of radioactive thiamine by healthy volunteers after varying oral doses of ^{35}S-thiamine hydrochloride*

Oral dose of radioactive thiamine (mg.)	*Radioactivity per cent of oral dose*	*Thiamine, mean weight (mg.)*
1.0	51.0 ± 2.07	0.51 ± 0.02
2.0	46.7 ± 4.47	0.93 ± 0.09
2.5	39.2 ± 5.07	0.98 ± 0.12
3.3	44.4 ± 3.76	1.47 ± 0.12
5.0	35.5 ± 1.77	1.77 ± 0.09
10.0	43.3 ± 6.63	4.33 ± 0.66
20.0	23.8 ± 1.51	4.77 ± 0.36
50.0	11.3 ± 1.81	5.63 ± 0.90

Results are expressed as the mean ± S.E.M. Urine was collected for 72 hours.
*Subjects were given 200 mg. of thiamine hydrochloride intravenously at the time of the oral dose.

5. Individual variation is great - Mean absorption of 1 mg dose is 50% (range = 35-85%) therefore individual efficiency of absorption may be an important determinant of individuals B_1 requirement (38)

6. Fate of Absorbed Thiamine (Ref 39)
   a. Most of the absorbed thiamine is phosphorylated before it is stored in the liver (some also in kidney).
   b. Later the thiamine is dephosphorylated. The free thiamine is released for use by other tissues where it is again phosphorylated.
   c. Excess above that stored is metabolized or excreted (mainly) in the urine as free thiamine.
   d. The rbc's may receive TPP as such from the hepatic cells during passage through the liver.
   e. Total body storage is meager (25 to 30mg) in relation to daily needs (circa 1.23 mg)

B. EFFECT OF PRIMARY MALABSORPTION BEFORE AND AFTER TREATMENT WITH A GLUTEN FREE DIET ON THE INTESTINAL ABSORPTION OF THIAMINE (Ref 38)

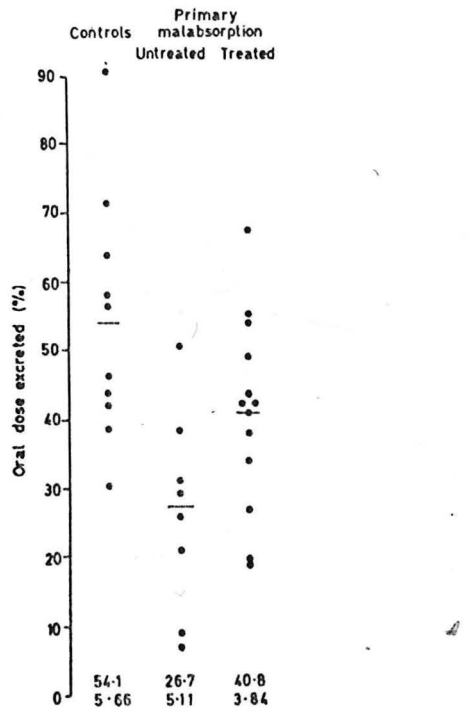


FIG. 3. Thiamine absorption in various clinical states.

C. ACHLORHYDRIA AND LARGE DOSES OF ANTACIDS (Ref 33, 45)

These older studies indicate significant decrease in thiamine absorption under these circumstances. The studies should be repeated with more modern techniques.

D. FOLATE DEFICIENCY (Ref 46)

Recent evidence by Schenker and co-workers reveal that folate deficiency produces a 30-50% decrease in thiamine absorption at low dose levels but does not impair high dose level absorption.

E. EFFECTS OF ALCOHOL (Ref 40, 41, 47)

1. ABSORPTION IN CHRONIC ALCOHOLICS (40)

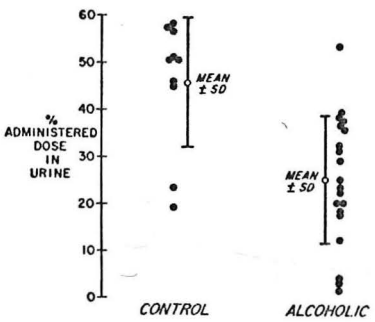


FIG. 1. Individual percentages of the thiamine dose recovered from the urine of the control and alcoholic subjects in 24 hr, shown with the mean and standard deviation for each group.

2. EFFECTS OF ETHANOL Per se ON ABSORPTION OF THIAMINE (41)

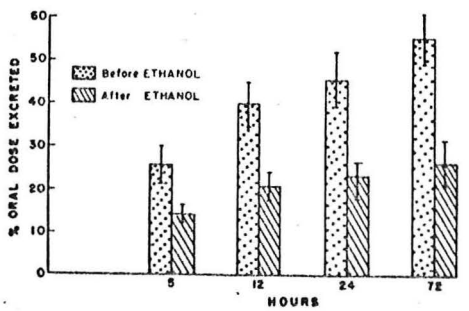


Fig. 1. The radioactivity in the serum and urine after administration of 5.0 mg. of radioactive thiamine orally to 3 healthy subjects with (- - ● - -) and without (— x —) prior administration of ethanol (1.5 Gm. per kilogram); 200 mg. of nonradioactive thiamine was given intravenously along with the oral dose.

F. EFFECTS OF LIVER DISEASE BEFORE AND AFTER 6-8 WEEKS OF TREATMENT WITH A HIGH PROTEIN NUTRITIOUS DIET (Ref 41)

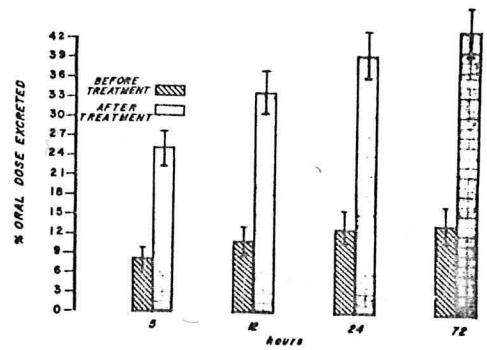


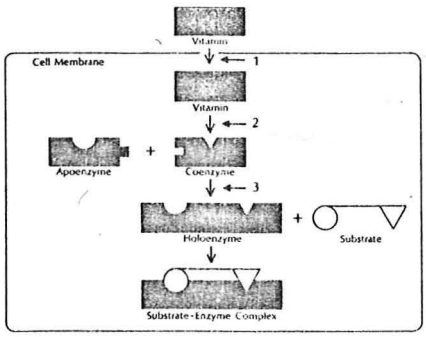
Fig. 3. The radioactivity in the serum (—▲—, —●—) and urine after administration of 5.0 mg. of radioactive thiamine orally to 12 malnourished alcoholic patients before and after treatment; 200 mg. of nonradioactive thiamine was given intravenously along with the radioactive thiamine.

III. DEFECTIVE UTILIZATION OF THIAMINE - FAULTY HOLOENZYME FORMATION OR ACTION (Ref 47-52)

A. LIVER DISEASE (Ref 48-52)

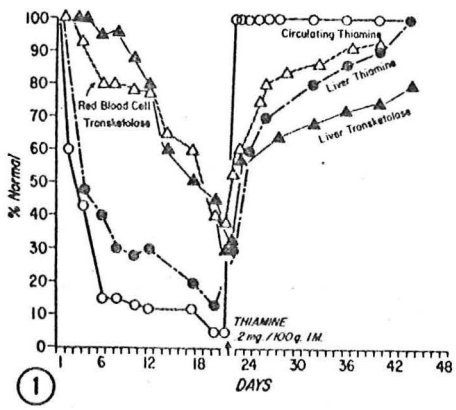
In addition to decreased absorption, diminished phosphorylation and storage of thiamine in alcoholics with liver disease, the conversion of thiamine diphosphate (coenzyme) into its metabolically active holoenzyme may also be impaired secondary to a deficiency of its apoenzyme.

1. HOLOENZYME FORMATION

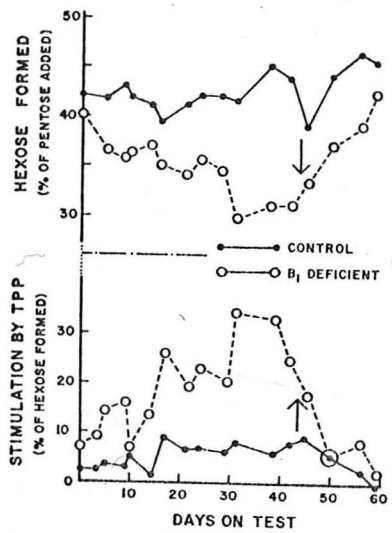


Several types of biochemical defects could lead to vitamin dependency, schematic suggests. These include: 1) defective transport of vitamin into cell, 2) defective conversion to coenzyme, 3) defective formation of holoenzyme due to apoenzyme mutation

2. CHANGES IN RBC AND LIVER TRANSKETOLASE DURING THIAMINE DEFICIENCY



3. CHANGES IN TRANSKETOLASE ACTIVITY DURING THIAMINE DEFICIENCY WITHOUT AND WITH THE ADDITION OF TDP (Ref 51)



4. CHANGES IN TRANSKETOLASE ACTIVITY IN THIAMINE DEFICIENT HUMAN SUBJECTS WITH AND WITHOUT LIVER DISEASE BEFORE AND AFTER ADDITION OF TDP (Coenzyme) (Ref 48, 49)

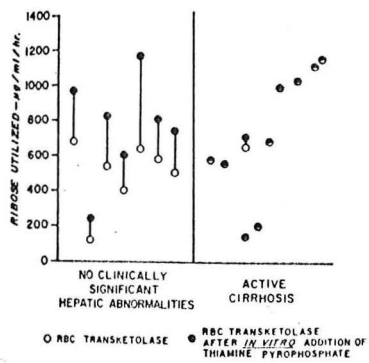


FIG. 1. Red blood cell-transketolase activity in alcoholics with thiamine deficiency and peripheral neuropathy.

B. MAGNESIUM DEFICIENCY

TRANSKETOLASE ACTIVITY AND TDP EFFECT IN COMBINED THIAMINE AND MAGNESIUM DEFICIENCY (Ref 51a)

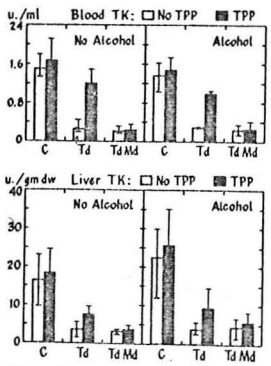


Fig. 5. Effect of in vitro addition of thiamine pyrophosphate *(TPP)* on blood and liver transketolase activity in thiamine-deficient and thiamine- and magnesium-deficient rats (Groups E_1 and E_2).

IV. DESTRUCTION OF THIAMINE IN THE G.I. TRACT (Ref 53-73)

A. ROLE OF BACTERIAL SYNTHESIS IN DETERMINING DAILY REQUIREMENTS OF THIAMINE (Ref 53-57)

This still debatable subject deserves re-examination by more modern technics. Nevertheless, the data of Najjar and Holt and of Takeuchi are impressive. The former found that when 9 subjects were put on a diet very low in thiamine (128 µg/day) four developed symptoms and signs of B_1 deficiency in 3-5 weeks whereas 4 other subjects did not develope evidence of B_1 deficiency even after 2-3 months on this low intake. There was a striking correlation between the amount of free thiamine in the feces and the development of evidence of thiamine deficiency. Those who developed evidence of B_1 deficiency excreted in the stool an average of 8.0 µg of thiamine per day whereas those who remained symptom free excreted 19 times that amount (158 µg/day)

TABLE 1.—*Output of Free and Combined Thiamine in Feces of Patients on a Completely Thiamine Free Diet*

(Figures represent micrograms excreted per day, an average of periods of one week's duration)

Subject	Symptoms of Thiamine Deficiency	Thiamine in Feces	
		Period 1	Period 2
		Free Thiamine	Free Thiamine
[redacted]	Present	9.8	8.5
[redacted]	Present	5.0	4.5
[redacted]	Present	4.7	5.5
[redacted]	Present	11.5	15.6
[redacted]	Questionable	26.0	
[redacted]	Absent	250	507
[redacted]	Absent	52	37
[redacted]	Absent	143	182
[redacted]	Absent	53	43

* Indicates thiamine liberated by treatment with clarase.

TABLE 2.—*Urinary Excretion of Thiamine Following Administration of Thiamine by Enema*

(Micrograms in twelve hour specimen)

Subject	Before Thiamine Enema	After Two Thiamine Enemas
A	160	1,615
B	162	5,200

Finally, Takeuchi's studies indicated that between 0.25 and 0.4 mg of the thiamine synthesized by intestinal bacteria are utilized by Japanese adults daily (57)

B. THE ROLE OF BACTERIAL DESTRUCTION OF THIAMINE IN THE GASTRO-INTESTINAL TRACT (Ref 58-60)

THIAMINASE DISEASE OF THE JAPANESE

In 1954 Matsukawa and Misawa isolated a new bacterium from the stool of a patient with beriberi which was capable of enzymatically cleaving thiamine into its pyrimidine and thiazole moieties and combining the pyrimidine moiety with an aromatic or heterocyclic amine. The new bacillus was named bacillus thiaminolyticus. A significant percent of patients whose stools contained bacillus thiaminolyticus were said to have "Thiaminase Disease".

Thiaminase Disease is characterized by:

1. Decreased thiamine content of the blood
2. Greater retention of thiamine during thiamine loading than control subjects (i.e.↓thiamine stores)
3. After saturation, when thiamine was given orally to patients with thiaminase disease, the recovery of thiamine in feces and stool was reduced (18%) compared to control subjects (85%)
4. A propensity to develope overt beriberi when strained by a high carbohydrate diet or marginal diet
5. Population surveys in Nigata and Kobe reveal a 3% incidence of bacillus thiaminolyticus in the stool whereas patients with beriberi had an incidence of 20%.

MATSUKAWA, CHANG ET AL. (ref 60)

Table IV
10 mg of thiamine are given orally for 7 successive days.

Case	Excreted in urine	Excreted in feces	Total
	%	%	%
I	4.8	8.3	13.1
II	11.5	4.3	15.8
III	12.5	11.8	24.3
IV	12.7	7.4	20.1
V	10.5	6.4	16.9
Average	10.4	7.6	18.0

Control subjects excreted 85% of the thiamine-about 20% in the urine and 65% in the stool.

C. THIAMINASE IN FOODS - LESSONS FROM ANIMAL DISEASES
CHASTEK PARALYSIS OF FOXES, CATS AND HORSES (Ref 61-73)

THE SAGA OF THE SILVER FOX

In 1932 an epidemic with a 38% mortality appeared in the silver fox farm of J.S. Chastek of Glencoe, Minnesota. Shortly thereafter epidemics in silver foxes were reported in Utah, Wisconsin, Sweden and Norway. From the early 30's to 1940's, Green, of the University of Minnesota, and Evans, from the U.S. Bureau of Biological Surveys, investigated these epidemics and at a time when the definitive proof that Wernicke's Encephalopathy was the consequence of thiamine deficiency was not yet in, they made the following important observations:

1. The epidemics occurred when fresh fish was added to the foxes usual ration (as little as ~10% fresh fish)
2. After 3 to 6 weeks on this diet the foxes developed ataxia, exquisite sensitivity to pain, paralysis of the limbs, convulsions and death
3. The pathologic findings were almost identical to that described in Wernicke's Disease
4. Chastek Paralysis did not occur
   a. if the fish was cooked
   b. if the fish was fed only on alternate days
   c. if B_1 were added in large amounts or if the foxes were treated with thiamine

They concluded that fresh fish either prevented the absorption of thiamine or destroyed it in the diet. They favored the latter hypothesis.

In the early 1940's Wooley and Krampitz of the Rockefeller Institute and Sealock and co-workers reported the presence of an enzyme, later named thiaminase, in fresh fish capable of rapidly destroying large amounts of thiamine. Wooley found the enzymatic activity to be distributed 2/8 in the head (gills mainly), 3/8 in the viscera, and 3/8 in muscle. Sealock found the activity mainly in head and viscera whereas Bhagrat and Devi found about 32% of total activity in muscle.

In 1956 Jubb and co-workers reported a spontaneous epidemic of Chastek Paralysis in cats fed a commerical cat food containing whole fish and cereal. From the early 1940's reports appeared identifying a thiaminase not only in many fresh and some salt water fish but also in crustacea, clams, oysters, crabs and in a variety of plant foods.

In 1951 Rees and his co-workers in England proved that the Mad-Staggers of Horses also known as Bracken Fern Staggers was the result of thiamine deficiency which produced a Wernicke's-like disease in horses. The air dried bracken fern contained a potent thiaminase.

D. THE ENIGMA OF THIAMINE DEFICIENCY IN RUMINANTS (Ref 94)

Once the microflora of ruminants is established, they no longer require dietary thiamine since the microorganisms in the rumen synthesize B_1 and other B vitamins. Veterinarians have been puzzled by the fact that cattle

and sheep in the U.S., England and Australia develop a disease similar to Wernicke's Encephalopathy known as Cerebrocortical Necrosis when ingesting plants containing a potent thiaminase.

Moreover, even though thiamine is still present in the rumen, these sick animals respond to massive doses of thiamine. In addition, dietary deprivation did not produce the clinical or pathological picture of Cerebrocortical Necrosis - even when large amounts of sodium sulfite was added to their ration to destroy some of the B_1 produced in the rumen.

The mystery was unraveled by the studies of Edwin, Lewis and Allcroft and of Pill, Davis and co-workers. They postulated that the thiaminase present in perennial rye grass and mouldy barley would cleave thiamine and combine the pyrimidine moiety with a naturally occurring base such as picolene. This new compound would then act as a metabolic antagonist to thiamine.

By feeding calfs a B_1 deficient diet and adding such a compound (Amprolium) they were able to reproduce the clinical and pathological picture of Cerebrocortical Necrosis of Ruminants.

This story may well have a clinical counterpart. It is known that the bulk of thiamine is absorbed in the upper 1/2 of the small bowel. Bacillus thiaminolyticus which produces Thiaminase Disease and is found in 20% of the cases of beriberi in Japan, is present in the lower 1/2 of the small bowel and in the large bowel. Since bacillus thiaminolyticus also splits thiamine into its pyrimidine and thiazole moieties and combines the pyrimidine to an aromatic or heterocyclic amine, it may by doing this also produce a metabolic antagonist of thiamine.

VI. POSSIBLE VITAMIN DEPENDENT STATES ASSOCIATED WITH AN INHIBITOR OF THIAMINE PYROPHOSPHATE - ADENOSINE TRIPHOSPHATE PHOSPHORYLTRANSFERASE IN URINE, BLOOD AND SPINAL FLUID

A. LEIGH'S DISEASE - SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY (SNE)

In 1972 Pincus reviewed 86 cases of SNE and the evidence (Cooper, Pincus and Itakawa) which indicates that SNE represents a genetic neurological disease resulting not from an enzyme deletion but from production of an inhibitor which prevents the enzymatic synthesis of thiamine triphosphate in the central nervous system.

SNE was first described by Leigh in 1951. Although originally considered a rare disease more than 86 cases have been reported. Pincus alone saw 10 cases in the past 18 months.

SNE is a degenerative disease of the CNS usually appearing before the age of two, although a few cases have been reported in teenagers and adults. There is great variability in the clinical picture. The following occur in varying combinations:

- Feeding problems
- Weakness and hypotonia
- Ophthalmoplegia
- Ataxia
- Nystagmus
- Cerebellar signs
- Convulsions
- Loss of vision
- Peripheral neuropathy
- Periods of hyperventilation
- Prolonged episodes of apnea

It appears to be an hereditary disorder of the autosomal recessive type. Incidence of SNE in siblings of affected children is 26.8%. The rate of consanguinity in the parents of affected children is high.

Pathological findings are characterized by necrotizing lesions with a characteristic distribution in the midbrain, lower brain stem, spinal cord, thalamic and dentate nuclei, basal ganglia, and optic nerves and tracts.

The resemblance to Wernicke's Disease has made students of SNE suspect and investigate the possibility that it represents a disturbance in thiamine metabolism. Usual doses of thiamine are without effect but several children have seemed to benefit from the use of pharmacological amounts of thiamine.

Moreover, the studies of Cooper, Pincus and Itakawa have disclosed that patients with SNE have in their blood, urine and spinal fluid an inhibitor of TDP - ATP phosphoryltransferase. Supporting the importance of this inhibitor is the evidence that at post mortem thiamine triphosphate was absent in the brain but present in liver and kidneys of such patients. In addition, the activities of all the TDP dependent enzymes were normal.

SPECIFICITY OF THE INHIBITOR

An appraisal of the specificity of the TPP-ATP phosphoryl transferase assay for SNE

	Number	*Inhibitory Assay*	
		Positive	*Negative*
Autopsy-proven cases of SNE	8	8	–
Living patients with SNE (autopsy in a sibling)	5	5	–
Patients suspected of SNE but proven to have other conditions	13	1	12*
Patients once suspected of SNE, now felt to have other conditions	10	–	10
Patients suspected of SNE, no diagnosis yet established	41	13	28

*These have included Werdnig Hoffman's disease, cerebral arteritis, Guillian-Barré syndrome, multiple sclerosis, metachromatic leukodystrophy, Barter's syndrome, tuberous sclerosis, progressive supranuclear ophthalmoplegia, Wernicke's encephalopathy and carbamyl phosphate transferase deficiency.

CONTENT OF THIAMINE TRIPHOSPHATE (TTP), DIPHOSPHATE (TDP), MONOPHOSPHATE (TMP) AND FREE THIAMINE IN THE BRAIN OF A PATIENT WITH SNE AND CONTROLS

Sample	TTP	TPP	TMP	T
		Cerebellum		
SNE	0.1*	78.0	8.0	14.0
		Frontal lobe		
SNE	0.1*	77.7	14.5	7.8
Normal (A)	12.4	72.3	4.3	11.0
Normal (B)	6.9	76.6	11.2	5.3
Normal (E)	9.9	58.0	14.8	17.3
		Liver		
SNE	9.7	76.2	5.1	9.0
Normal (B)	6.7	77.3	8.0	8.0
Normal (C)	4.9	74.4	8.5	12.2
Normal (D)	6.4	75.2	10.6	7.8
Normal (E)	6.5	63.6	14.0	15.9
		Kidney		
SNE	6.6	64.6	24.1	4.7
Normal (B)	5.1	69.4	9.2	16.3
Normal (C)	5.0	71.6	4.5	18.2
Normal (E)	8.6	47.3	19.4	24.7

* Below the limit of significance.

B. ONDINE'S CURSE - FAILURE OF AUTOMATIC CONTROL OF RESPIRATION (Ref 82-87)

Ondine's Curse refers to that form of alveolar hypoventilation with no explanation save for CNS abnormality in the automatic control of respiration. As of 1970 only 30 patients were reported in the literature. However, in 1972 Lonsdale and Mercer, from the section of biochemical genetics of the Cleveland Clinic, reported 4 more cases. Most cases in the past were not apparent until the third decade of life. More recently cases have been reported in neonates and adolescents.

In many cases apnea occurs only during sleep and attacks of apnea may be set off by mild upper respiratory infections. In SNE episodes of apnea are also common and they are similarly precipitated by mild infections.

In 1972, Lonsdale and Mercer using more sophisticated tools for intensive investigation reported 4 cases of Ondine's Curse, 3 of the 4 patients excreted in their urine a substance exhibiting a highly characteristic but unidentified ninhydrin staining chromatogram when the urine was subjected to high voltage electrophoresis and ascending chromatography.

In 2 of the 4 patients the urine was also positive for the inhibitor of thiamine diphosphate-adenosine triphosphate phosphoryl transferase. In one case the mother of the affected child also had the inhibitor in her urine.

According to Pincus 3 of 5 cases with Ondine's Curse had a post mortem neuropathological findings closely resembling SNE in both the nature and the distribution of the lesions. (74)

A clinical trial in one neonate with Ondine's Curse of pharmacological amounts of thiamine promptly abolished the recurrent episodes of apnea. Moreover, the child has remained free of apneic periods up to the present. This case raises the important and neglected problem of crib death syndrome which could occasionally be triggered by a viral illness and treated effectively with thiamine. (83)

VII. NEW THERAPEUTIC FORMS OF THIAMINE

For the past 15 years Japanese investigators have been seeking new forms of thiamine which might be absorbed more effectively and enter cells more efficiently than thiamine hydrochloride or nitrate, the compounds used exclusively in this country. In this regard they have been eminently successful. In Japan, for the past several years, two new forms of thiamine have had widespread use because of their ability to produce higher blood, tissue and cerebrospinal fluid levels of thiamine.

Kinetics of thiamine hydrochloride absorption indicate that it is rate limited. The higher the oral dose, the smaller the percent of the dose absorbed. Moreover, it appears to enter cells by an active process so that tissue levels are not proportional to blood levels.

The two new forms of thiamine are absorbed in proportion to the oral dose administered and since they enter cells by passive diffusion not only are higher blood levels achieved but higher tissue and cerebrospinal fluid levels are found.

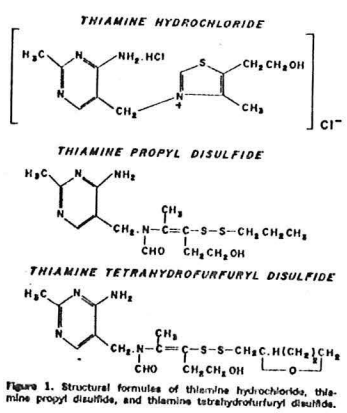
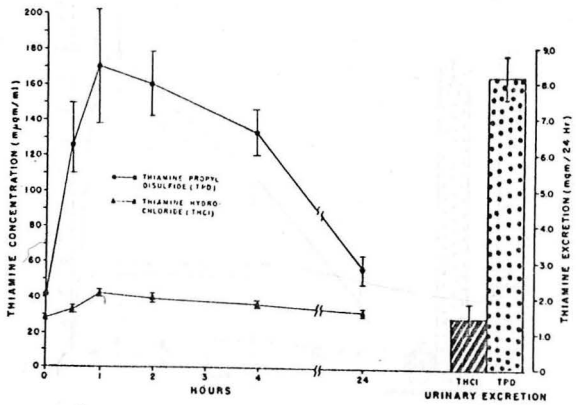


Figure 1. Structural formulas of thiamine hydrochloride, thiamine propyl disulfide, and thiamine tetrahydrofurfuryl disulfide.

COMPARISON OF ABSORPTION OF A 50 MG DOSE OF THIAMINE HYDROCHLORIDE AND PROPYL DISULFIDE IN NORMAL SUBJECTS



COMPARISON OF ABSORPTION OF 10 TO 50 MG DOSES OF THIAMINE HYDROCHLORIDE AND PROPYL DISULFIDE

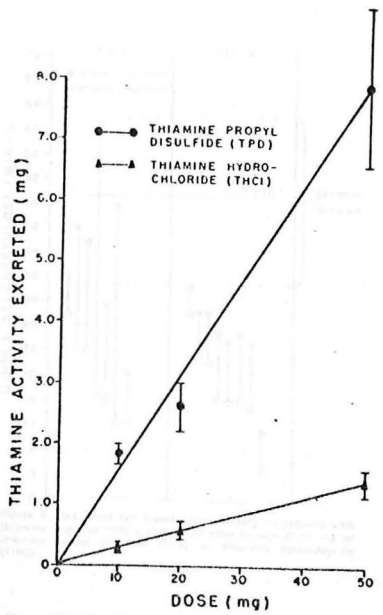
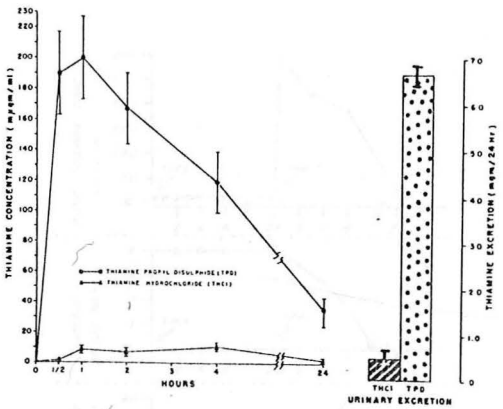


Figure 4. Relationships between the amount of oral administration of thiamine hydrochloride or thiamine propyl disulfide and the urinary excretion of thiamine.

COMPARISON OF THE ABSORPTION OF 50 MG OF THIAMINE HYDROCHLORIDE AND PROPYL DISULFIDE GIVEN ORALLY IN MALNOURISHED ALCOHOLICS WITH FATTY LIVERS



EFFECT OF 50 MG THIAMINE HYDROCHLORIDE AND PROPYL DISULFIDE ON RBC TRANSKETOLASE IN THIAMINE DEPLETED SUBJECTS

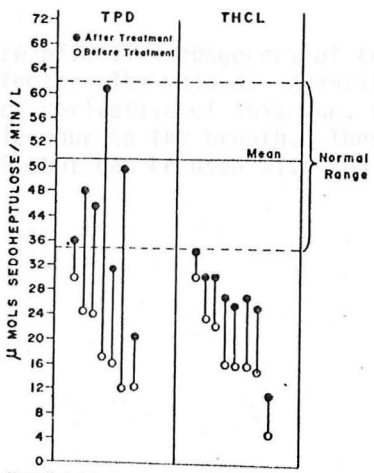


Figure 6. Red blood cell transketolase activity in patients with thiamine depletion before and 24 hr after receipt of 50 mg of thiamine propyl disulfide (*TPD*) or thiamine hydrochloride (*THCl*).

COMPARISON OF THE EFFECTS OF THIAMINE PROPYL DISULFIDE AND HYDROCHLORIDE ON BLOOD THIAMINE, CEREBROSPINAL FLUID AND CLINICAL RESPONSE IN WERNICKE'S SYNDROME

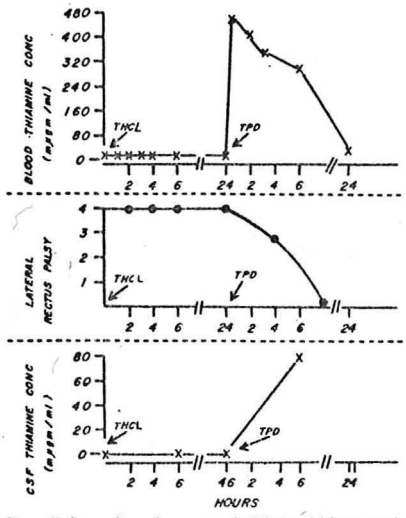


Figure 7. Comparison of response of clinical and laboratory abnormalities in thiamine-depleted alcoholics with Wernicke's encephalopathy after oral administration of 50 mg of thiamine hydrochloride (*THCl*) or thiamine propyl disulfide (*TPD*).

These new more effective congeners of thiamine have not produced any untoward side effects. The main disadvantage of thiamine propyl disulfide, an allium (garlic) derivative of thiamine, is the annoying side effect of producing a garlic odor to the breath. These compounds are not now available in the U.S.A. but can be used with FDA approval for investigational purposes.

REFERENCES

A. THIAMINE - BIOCHEMISTRY

1. Albersheim, P. and Bonner, J. Thiamine. Metabolic Pathways 2:617, 1961 (Chapter 21).

2. Lipmann, F. The Biochemical Functions of B Vitamins. Perspectives In Biol and Med 13:1, 1969.

3. Krampitz, L.O. Catalytic Functions of Thiamin Diphosphate. Ann Rev Biochem 38:692, 1969.

B. WERNICKE'S ENCEPHALOPATHY

4. DeWardener, H.E. and Lennox, B. Cerebral Beriberi (Wernicke's Encephalopathy) Lancet 1:11, 1947.

5. Cruickshank, E.K. Wernicke's Encephalopathy. Quart J Med 19:327, 1950.

6. Victor, M. and Adams, R.D. Metabolic and Toxic Disease of the Nervous System. Assoc Res in Mental Dis 32:526, 1952.

7. Denny-Brown The Neurological Aspects of Thiamine Deficiency. Federat Proc 17:35, 1958.

8. Alexander, L. Wernicke's Disease. Identity of Lesions Produced Experimentally by B_1 Avitaminosis in Pigeons With Hemorrhagic Polioencephalitis Occurring In Chronic Alcoholism in Man. Am J Pathology 16:61, 1940.

9. Victor, M., Adams, R.D. and Collins, G.H. The Wernicke-Korsakoff Syndrome. Contemporary Neurology Series #7. F.A. Davis Co., Philadelphia, 1971.

10. Victor, M. and Adams, R.D. On the Etiology of the Alcoholic Neurological Disease. Am J Clin Nutrit 9:379, 1961.

11. Mancall, E.L. Some Unusual Neurologic Diseases Complicating Chronic Alcoholism. Am J Clin Nutrit 9:404, 1961.

12. Dreyfus, P.M. and Victor, M. Effects of Thiamine Deficiency on the Central Nervous System. Am J Clin Nutrit 9:414, 1961.

13. McCandless, D.W. and Schenker, S. Encephalopathy of Thiamine Deficiency: Studies of Intracerebral Mechanisms. J Clin Invest 47:2268, 1968.

14. Phillips, G.B., Victor, M., Adams, R.D. and Davidson, C.S. A Study of the Nutritional Defect in Wernicke's Syndrome. J Clin Invest 31:859, 1952.

15. Shimojyo, S., Scheinberg, P. and Reinmuth, O. Cerebral Blood Flow and Metabolism in the Wernicke-Korsakoff Syndrome. J Clin Invest 46:849, 1967.

16. Gravallese, M.A. Jr. and Victor, M. Circulatory Studies in Wernicke's Encephalopathy. Circulation 15:836, 1957.

17. Birchfield, R.I. Postural Hypotension in Wernicke's Disease: A Manifestation of Autonomic Nervous System Involvement. Am J Med 36:404, 1964.

18. Philip, G., and Smith J.F. Hypothermia and Wernicke's Encephalopathy. Lancet 2:122, 1973.

19. Freund, G. Chronic Central Nervous System Toxicity of Alcohol. Ann Rev Pharm 13:217, 1973.

20. Drenick, E.J. et al. Occurrence of Acute Wernicke's Encephalopathy During Prolonged Starvation for the Treatment of Obesity. NEJM 274:937, 1966.

21. Shah, N. and Wolff, J.A. Thiamine Deficiency: Wernicke's Encephalopathy Successfully Treated in a Child with Acute Leukemia. Pediatrics 51:4, 1973.

22. Lopez, R.I. and Collins, G.H. Wernicke's Encephalopathy, A Complication of Chronic Hemodialysis. Arch Neurol 18:248, 1968.

23. Faris, A.A. Wernicke's Encephalopathy in Uremia-Neurology 22:1293, 1972.

C. VITAMIN DEPENDENT GENETIC DISORDERS

24. Scriver, C.R. Vitamin-responsive Inborn Errors of Metabolism. Metabolism 22:1319, 1973.

25. Rosenberg, L.E. Vitamin-Dependant Genetic Disease. Hospital Practice, July 1970, 59-67.

26. Harris, H. Enzyme and Protein Polymorphism in Human Populations. Br Med Bull 25 :5, 1969.

D. VITAMIN REQUIREMENTS AND STORES

27. Ziporin, Z.Z. et al. Thiamine Requirements in Adult Humans as Measured by Urinary Excretion of Thiamine Metabolites. J Nutrition 85:297, 1965.

28. Ziporin, Z.Z. et al. Excretion of Thiamine and its Metabolites in the Urine of Young Adult Men Receiving Restricted Intakes of the Vitamin. J Nutrition 85:287, 1965.

29. Williams, R.H. and Bissell, G.W. Thiamine Metabolism Arch Int Med 73:203, 1944.

30. Holt, E.L. Jr. The Thiamine Requirements of Man. Fed Proc 3:171, 1944.

31. Fats and Thiamine Requirements. Nutrition Rev 23:334, 1965.

32. Takeda, J. Distribution of Thiamine in Human Organs. Niigata Med J 61:478, 1947.

33. Ingelfinger, F.J. The Parenteral Use of Vitamin Preparations. NEJM 233:379, 1945.

34. Ferrebee, J.W., Weisman, N., Parker, D. and Owen, P.S. Tissue Thiamin Concentrations and Urinary Thiamin Excretion. J Clin Invest 21:401, 1942.

35. Gellene, R. et al. B-Complex Vitamins in Total Food Deprivation. Federation Proc 242(2):314, 1965.

E. INTESTINAL ABSORPTION OF THIAMINE - NORMAL AND DEFECTIVE

36. Rindi, G. and Ventura, U. Thiamine Intestinal Transport. Physiology Rev 52:821, 1972.

37. Middleton, E.J. and Grice, H.C. Vitamin Absorption Studies IV Site of absorption of C14-Riboflavin and S-35-Thiamine in the Rat. Canad J Biochem 42:353, 1964.

38. Thomson, A.D. The Absorption of S-35-Thiamine Hydrochloride in Control Subjects and in Patients with Intestinal Malabsorption.

39. Williams R.H. and Bissell, G.W. Thiamine Metabolism. Arch Int Med 72:203, 1944.

40. Tomasulo, P.A., Kater, R.M.H. and Iber, F.L. Impairment of Thiamine Absorption in Alcoholism. Am J Clin Nut 21:1340, 1968.

41. Thomson, A;D., Baker, H. and Leevy C.M. Patterns of S-35-Thiamine Hydrochloride Absorption in the Malnourished Alcoholic. J Lab Clin Med 76:34, 1970.

42. Halsted, C.H., Griggs, R.C. and Harris, J.W. The Effect of Alcoholism on the Folic Acid (H^3-PGA) Evaluated by Plasma Levels and Urine Excretion. J Lab Clin Med 69:116, 1967.

43. Dann, M. and Cowgill, G.R. Influence of Diarrhea on Vit B_1 Requirement. Arch Int Med 62:137, 1938.

44. Robinson, W.D. et al. Urinary Excretion of Thiamin in Clinical Cases and Value of Such Analysis in Diagnosis of Thiamine Deficiency. J Clin Invest 19:399, 1940.

45. Brummer, P. and Markkanen, T. Urinary Excretion of Thiamine and Riboflavin in Achlorhydria. Acta Med Scand 166:75, 1960.

46. Howard, L., Wagner, C. and Schenker, S. Malabsorption of Thiamine in Folate Deficient Rats. Clin Res 22:583A, 1974.

47. Leevy, C.M. and Baker, H. Vitamins and Alchohol. the Am J Clin Nutrit 21:1325, 1968.

F. DEFECTIVE UTILIZATION - FAULTY HOLOENZYME FORMATION OR ACTION

48. Fennelly, J.J., Baker, H., Frank, O., and leevy C.M. Deficiency of Thiamine Pyrophosphate Apoenzyme in Liver Disease. Clin Res 11:182, 1963.

49. Fennelly J.J., Baker, H., Frank, O. and Leevy, C.M. Red Blood Cell - Tranketolase Activity in Malnourished Alcoholics with Cirrhosis. the Amer J Clin Nutrit 20:946, 1967.

50. Cole, M., Turner, A., Frank, O., Baker H. and Leevy C.M. Observations on Thiamine Metabolism in Wernicke's Encephalopathy. Am J Clin Nutrit 18:303, 1966.

51. Brin, M., Tai, M. Ostashever, A.S. and Kalinsky, H. The Effect of Thiamine Deficiency on the Activity of Erythrocyte Hemolysate Transketolase. J Nutrition 71:273, 1960.

51a. Zieve, L. et al. Effects of Magnesium Deficiency on Blood and Liver Transketolase and On Recovery of Enzyme Activity in B_1-deficient rats Receiving B_1. J Lab and Clin Med 72:268, 1968.

52. Cole, M., Leevy, C.M. et al. Observations on Thiamine Metabolism in Wernicke's Encephalopathy. Am J Clin Nutrit 18:303, 1966.

G. PRODUCTION AND DESTRUCTION OF THIAMINE IN THE GI TRACT

53. Najjar, V.A. and Holt, L.E. The Biosynthesis of Thiamine in Man and its Implications in Human Nutrition. JAMA 123:683, 1943.

54. Denko, C.W. et al. The Excretion of B-Complex Vitamins by Normal Adults on a Restricted Diet.

55. Benesch, R. Synthesis and Destruction of Nicotinic Acid by the Mixed Caecal Flora of Man. Lancet 1:718, 1945.

56. Williamson, A. and Parsons, H.T. Some Factors Influencing the Fecal Excretion of Thiamine by Human Subjects. J of Nutrition 29:51, 1945.

57. Takeuchi, T. Utilization of B_1 and B_2 biosynthesized in the Intestinal Tract In Japanese Adults. Vitamins (Japan) 6:269, 1953.

58. Thiaminase Disease - Nutrition Rev 14:166, 1956.

59. Hayashi, R. Bacterial Synthesis and Destruction of Thiamine. Nutrition Rev 15:65, 1957.

60. Matsukawa, S., Chang, S., Misawa, H., Fujimiya, M., Kobayashi, N., Horikawa, Y. and Takato, K. Studies on the Thiamine Deficiency Due to Bacterial Thiaminase 1. Investigations on Intestinal Contents. J. Vitaminology 1:43, 1954.

61. Green, R.G., Carlson, W.E. and Evans, C.A. A Deficiency Disease of Foxes Produced by Feeding Fish: B_1 Avitaminoses Analagous to Wernicke's Disease of Man. J Nutrition 21:243, 1941.

62. Evans, C.A., Carlson, W.E. and Green, R.F. The Pathology of Chastek Paralyses in Foxes: A Counterpart of Wernicke's Hemorrhagic Polioencephalitis of Man. Am J Path 18:79, 1972.

63. Green, R.G., Carlson, W.E. and Evan, C.A. The Inactivation of B_1 in Diets Containing Whole Fish. J of Nutrition 23:165, 1942.

64. Wooley, D.W. and Krampitz, L.O. The Manner of Inactivation of Thiamine by Fish Tissue. J Biol Chem 152:9, 1944.

65. Deutsch, H.F. and Hasler, A.D. Distribution of Vit B_1 Destructive Enzyme in Fish. Proc Soc Exper Biol and Med 53:63, 1943.

66. Sealock, R.R., Livermore, A.H., and Evans, C.A. Thiamine Inactivation by Fresh Fish or Chastek-Paralysis Factor. J Am Chem Soc 65:953, 1943.

67. Owen, P.S. and Ferrebee, J.W. The Anti-Thiamine Factor in Fish. NEJM 229:435, 1943.

68. Smith, D.C. and Proutt, L.M. Development of Thiamine Deficiency n the Cat on a Diet of Raw Fish. Proc Soc Exp Biol Med 56:1, 1944.

69. Jubb, K.V., Saunders, L.Z., and Coates, H.V. Thiamine Deficiency Encephalopathy in Cats. J Comp Path 66:217, 1956.

70. Wesig, P.H., Freed, A.M., Haag, J.R. Antithiamine Activity of Plant Materials. J Biol Chem 165:737, 1946.

71. Evans, R.E.T., Evans, W.C. and Roberts, H.E. Studies on Brachen Poisoning in the Horse. Brit Veterin Jour 107:364, 1951 and 107:399, 1951.

72. Bhagvat, K. and Devi, P. Inactivation of Thiamine by Certain Foodstuffs and Oil Seeds. Indian J Med Res 32:131, 1944.

73. Yudkin, W.H. Thiaminase, the Chastek-Paralysis Factor. Physiolog Rev 29:389, 1949.

H. POSSIBLE VITAMIN DEPENDENT STATES ASSOCIATED WITH AN INHIBITOR OF TPP-ATP PHOSPHORYL TRANSFERASE IN URINE AND BLOOD

74. Pincus, J.H. Subacute Necrotizing Encephalomyelopathy (Leigh's Disease): A Consideration of Clinical Features and Etiology. Devel Med Child Neurol 14:87, 1972.

75. Cooper, J.R., Itokawa, Y. and Pincus, J.H. Thiamine Triphosphate Deficiency in Subacute Necrotizing Encephalomyelopathy. Science 164:74, 1969.

76. Pincus, J.H., Itokawa, Y. and Cooper, J.R. Enzyme-Inhibiting Factor in Subacute Necrotizing Encephalomyelopathy. Neurology 19:841, 1969.

77. Cooper, J.R., Pincus, J.H., Itokawa, Y. and Piros, K. Experience with Phosphoryl Transferase Inhibition in Subacute Necrotizing Encephalomyelopathy. NEJM 283:793, 1970.

78. Simopoulos, A., Roth, J.A., Golde, D.W. and Bartter, F.C. Subacute Necrotizing Encephalomyelopathy with Vacuolated Cells in the Bone Marrow. Neurology 22:1257, 1972.

79. Sheramata, W.A., Cooper, J.R. and Joseph, J. Leigh's Disease: Response to High Dose Thiamine Therapy. Neurology 21:456, 1971.

80. Sipe, J.C. Leigh's Syndrome: The Adult Form of Subacute Necrotizing Encephalomyelopathy with Predilection for the Brainstem. Neurology 23:1030, 1973.

81. Pincus, J.H., Cooper, J.R., Itokawa, Y. and Gumbinas, M. Subacute Necrotizing Encephalomyelopathy. Effects of Thiamine and Thiamine Propyl Disulfide. Arch Neurol 24:511, 1971.

82. Mellins, R.B. et al. Failure of Automatic Control of Ventilation (Ondine's Curse). Medicine 49:487, 1970.

83. Lonsdale, D. and Mercer, R.D. Prinary Hypoventilation Syndrome. Lancet 2:487, 1972.

84. Kryger, M. et al. The Sleep Deprivation Syndrome of the Obese Patient. A Problem of periodic Nocturnal Upper Airway Obstruction. Am J Med 56:531, 1974.

85. Dement, W.C. and Guilleminault, C. Sleep Disorders: The State of the Art. Hosp Practice, Pg 57, Nov. 1973.

86. Lugaresi, E. et al. Effect of Tracheostomy in Two Patients with Hypersomnia and Periodic Breathing. J Neurol Neurosurg Psych 36:15, 1973.

87. Giraudoux, J. Ondine, a Romantic Fantasy in Three Acts. English Version by M. Valency, Samuel French, Inc., N.Y., 1956.

I. NEW THERAPEUTIC FORMS OF THIAMINE

88. See Pincus ref 73.

89. See Pincus ref 80.

90. Thomson, A.D., Frank, O., Baker, H. and Leevy, C.M. Thiamine Propyl Disulfide: Absorption and Utilization. Ann Int. Med 74:529, 1971.

J. UNUSUAL USE OF THIAMINE

91. Shannon Prevention of Flea Bites with Thiamine. Minnesota Med 26:799, 1943.

92. Eder, H.L. Flea Bites: Prevention and Treatment with Thiamine Chloride. Arch Pediatrics 62:300, 1945.

K. LATE ARRIVALS

93. Dreyfuss, P.M. Thoughts on the Pathophysiology of Wernicke's Disease. Ann N Y Acad Sci 215:367, 1973.

94. Thiamine Deficiency In Ruminants. Nutrition Reviews 27:176, 1969.