MEDICAL GRAND ROUNDS
UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER
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WERNICKE'S ENCEPHALOPATHY - REVISITED

- AN UPDATE -

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INTRODUCTION

Since recent evidence indicates that Wernicke's encephalopathy usually escapes clinical detection even in university hospitals and frequently is not diagnosed until the patient reaches the autopsy table, a critical review of the subject of Wernicke's encephalopathy is timely.

Acute thiamine deficiency is the cause of the Wernicke-Korsakoff syndrome. The original triad of symptoms described by Wernicke (1881) consisted of clouding of consciousness, ataxia and ophthalmoplegias.

Korsakoff psychosis is characterized by an abnormal mental state in which memory and learning are affected out of proportion to the other cognitive functions in an otherwise alert and responsive patient.

Victor, Adams & Collins (1971) broadened the diagnostic features and defined Wernicke's encephalopathy as a neurological disorder of acute onset characterized by nystagmus, abducens and conjugate palsies, ataxia of gait and a global confusional state occurring together or in various combinations. It should be noted that only 2 of the 229 subjects with Wernicke's encephalopathy reported by Victor et al 1971 were non-alcoholics.

There is now ample evidence that the clinical conception of Wernicke's encephalopathy must be broadened even further (Lishman, 1981). The condition is seriously underdiagnosed not only in alcoholics with which it is commonly associated but also in a large variety of disorders occurring in non-alcoholics which are characterized by malnutrition and inadequate intake of thiamine (Harper, 1981 & 1983: Ebels, 1974).

I. THIAMINE - ROLES IN METABOLISM

A. FORMS OF THIAMINE IN THE BODY

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

2. THIAMINE TRIPHOSPHATE - TTP
   Synthesized from TDP and ATP by the enzyme TDP-ATP phosphoryltransferase
   TDP + ATP $\xrightarrow{Mg^{++}}$ TTP + ADP
   Constitutes 10% of Body Thiamine

3. THIAMINE MONOPHOSPHATE (TMP)
4. FREE THIAMIME

> 10% Body Thiamine

B. ACTIONS OF THIAMINE

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

2. OTHER FORMS OF THIAMINE WITH A PROPOSED COENZYME-INDEPENDENT ROLE IN THE NERVOUS TISSUE
   a. TTP is the neurophysiologically active form of thiamine. (Cooper et al)
   b. TTP important in the binding of TDP to its apoenzyme (Yusa & Maruo)

II POSSIBLE PATHOGENIC MECHANISMS IN WERNICKE'S ENCEPHALOPATHY-PROS AND CONS

A) DECREASED TRANSKETOLASE ACTIVITY INHIBITS PENTOSE PHOSPHATE PATHWAY, IN TURN INHIBITING NADPH SYNTHESIS REQUIRED FOR MYELIN FORMATION.

i. Transketolase activity falls in brain with thiamine deficiency.
ii. Altered kinetic property of transketolase (Blass and Gibson, 1977).

but

iii. Pentose phosphate cycle in brain not impaired with thiamine deficiency (McCandless et al, 1976).
iv. Neurological symptoms of thiamine deficiency are reversed rapidly with thiamine administration, transketolase activity being only slightly improved (McCandless and Schenker, 1968).
v. Neurological recovery after thiamine administration is much more rapid than turnover of myelin components.

B) DECREASED PYRUVATE DECARBOXYLASE AND α-KETOGLUTARATE DECARBOXYLASE ACTIVITIES INTERFERE WITH CEREBRAL ENERGY METABOLISM BY DEPRESSION OF THE KREBS CYCLE.

i. Pyruvate decarboxylase activity falls in brain in thiamine deficiency, with increased pyruvate concentrations, both these changes reverting to normal after thiamine therapy.

but

ii. ATP concentrations in brains of thiamine deficient animals appear normal (McCandless and Schenker, 1968; McCandless et al., 1976).

C) DECREASED PYRUVATE DECARBOXYLASE ACTIVITY DECREASES ACETYL CoA FORMATION, IN TURN DECREASING ACETYLCHOLINE SYNTHESIS.

i. Hemicholinum-3 induced acetylcholine depletion does alter consciousness in rats (Freeman, 1975).

but

ii. Acetylcholine concentrations appear norman in thiamine deficiency with only a small decrease in turnover (Vorhees et al., 1977)

D) THIAMINE DEPLETION INTERFERES WITH THIAMINE-DEPENDENT NEUROPHYSIOLOGICAL PROCESSES.

i. Thiamine triphosphate (TTP) is localized to nerve membranes and is released with nerve stimulation (Cooper et al., 1963; Cooper and Pincus, 1967; Barchi and Braun, 1972).

but

ii. TTP concentration does not fall in brains in thiamine deficient rats (Pincus and Grove, 1970).
iii. Changes in TTP in brain upon electrical stimulation have not always been found (Berman and Fishman, 1975).

from Thomson, Ryle and Shaw, 1983

III. THIAMINE REQUIREMENTS AND STORAGE

A. OFFICIAL RECOMMENDATIONS FOR THE HUMAN ADULT

FAO/WHO	0.4 mg per 1000 KCal
Food and Nutrition Board of NAS-NRC	0.5 mg per 1000 KCal

Ref. Woman - 2300 KCal - 1.2 mg/day Ref. man 3000 KCal 1.5 mg./day

According to the Hanes I and II Surveys in general the population of the USA has an adequate thiamine intake, most likely contributed to by B_1 fortification of bread, cereals and milk. At all decades from the first through the seventh the intake of thiamine was found to be in excess of 0.6 mg per 1000 KCal. However, especially in the elderly both free living and institutionalized there are significant pockets of deficiency.

THIAMINE STATUS IN THE ELDERLY

Age, mean or range	Site	Living status	Method	Fraction-deficient		
				severe %	marginal %	adequate %
60–83	Maryland	nursing home	blood thiamin	?	11	89
60–83	Virginia	free-living	blood thiamin	10	15	75
70	New York State	free-living	TPP effect[1]	3	17	80
68		VA Hospital	TPP effect	7	31	62
62–96	New York State	nursing home ill	TPP effect	10	30	60
			urine thiochrome	50	50	
62–99	Colorado	home and nursing home	urine thiochrome	37	14	73
62–98	Colorado	nursing home	urine thiochrome		19	71
> 65	Vancouver	free-living	urine thiochrome			100
65–94	Belfast	geriatric hospital		1	11	88
65–95	Belfast	nursing home	TPP effect	2	19	79
65–91	Belfast	free-living			12	88
81	England	free-living	TPP effect	15	53	32
72	Helsinki	old age home	TPP effect		45	55
65–93	Netherlands	hospital	TPP effect	6	25	69

From Baum & Iber, 1984

B. STORAGE OF THIAMINE IN THE BODY

Total body stores are small i.e. 25-30mg (Takeda, 1947) especially in relation to daily needs. Signs of thiamine deficiency appear in a population when intake falls <u>below</u> 0.3 mg/1000 KCal(Sauberlich et al., 1979).

Because of the high daily requirements, coupled with the small body stores, normal subjects on a thiamine free diet can develope clinical beriberi in a period of 9 to 27 days.

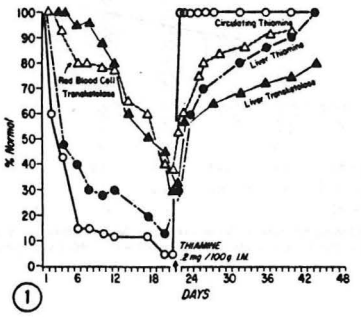
In malnourished subjects with depletion of body stores without overt clinical manifestations acute cerebral beriberi (Wernicke's Encephalopathy) or acute cardiovascular beriberi (Shoshin) can be precipitated in hours to a few days by the administration of I.V. glucose solutions.

IV. ASSESSMENT OF THIAMINE NUTRITIONAL STATUS

A. TESTS OF THIAMINE NUTRITIONAL STATUS

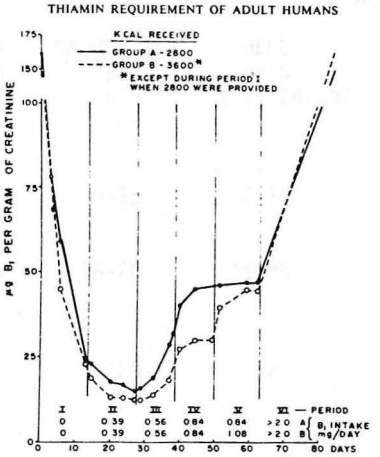
1. Blood thiamine levels
2. Urine thiamine excretion
3. Erythrocyte transketolase activity
4. Thiamine diphosphate stimulating effect on transketolase activity

B. SEQUENTIAL CHANGES IN BLOOD AND LIVER THIAMINE AND IN LIVER AND ERYTHROCYTE TRANSKETOLASE DURING EXPERIMENTAL THIAMINE DEPRIVATION AND REPLETION



From Fennelly et al, 1964

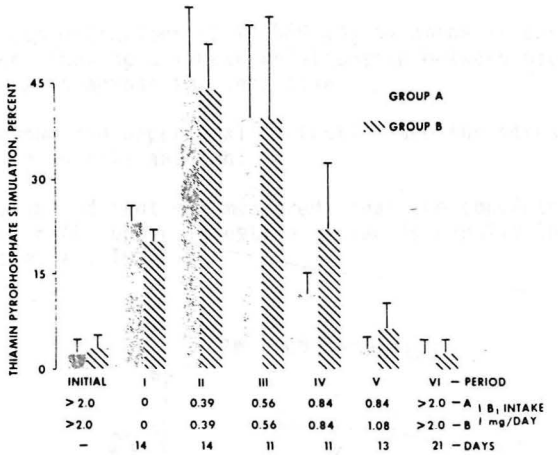
C. SEQUENTIAL CHANGES IN URINARY THIAMINE EXCRETION IN NORMAN ADULTS DURING A THIAMINE DEFICIENT DIET



Relationship of thiamin and caloric intakes to the urinary excretion of thiamin expressed as per gram of creatinine. During period VI, both groups received ad libitum diets.

from Sauberlich et al, 1979

D. SEQUENTIAL CHANGES IN THIAMINE DIPHOSPHATE STIMULATING EFFECT ON RBC TRANSKETOLASE ACTIVITY DURING EXPERIMENTAL THIAMINE DEFICIENCY



The effects of level of thiamin and caloric intakes on the thiamin pyrophosphate stimulation effect on erythrocyte transketolase activity. See Table 3 for information as to caloric intake levels. SD indicated.

Sauberlich et al, 1979

E. GUIDELINES IN USE FOR INTERPRETATION OF THE THIAMINE PYROPHOSPHATE (TPP) STIMULATING EFFECT IN ASSESSMENT OF THIAMINE STATUS IN ADULTS

	THIAMINE PYROPHOSPHATE EFFECT - PERCENT INCREASE IN TRANSKETOLASE ACTIVITY				
	BRIN 1976 USA	SAUBERLICH 1967 USA	HELL 1976 SWITZERLAND	HELLER 1974 W. GERMANY	BONI 1980 BELGIUM
ACCEPTABLE (LOW RISK) OR NORMAL (ADEQUATE)	0-15	0-15	0-15	0-19	0-18
LOW (MEDIUM RISK) OR MARGINALLY DEFICIENT (SUBCLINICAL)	15-25	16-20	15-25	20-22	> 18
DEFICIENT (HIGH RISK) OR SEVERELY DEFICIENT	>25	>20	>25	>23	

V. ABSORPTION OF THIAMINE

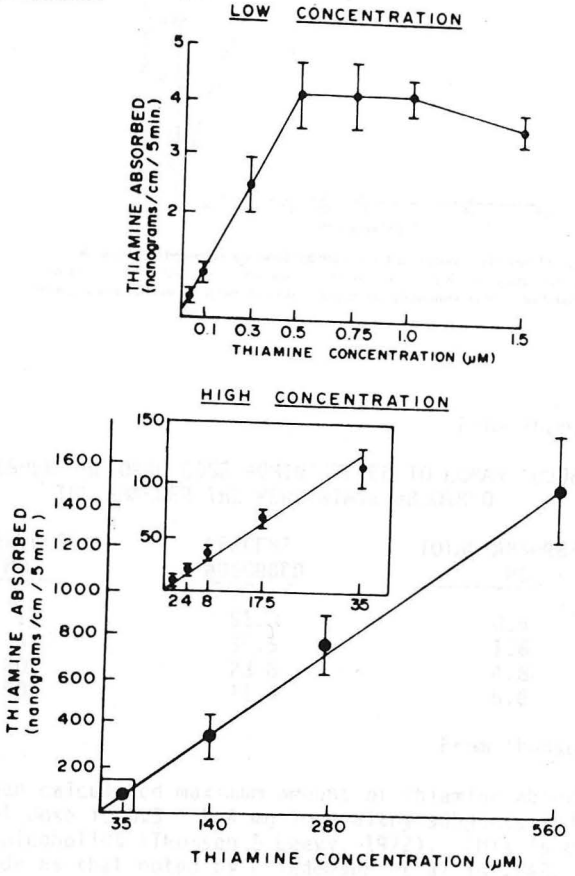
A. STUDIES IN ANIMALS - (Rindi & Venture, 1972; Hoyumpa et al 1975)

1. At low concentrations thiamine (less than 1.5 µM) is absorbed in the small intestine by an active process showing saturation kinetics.

2. At high concentrations (2 to 560 µM) thiamine is absorbed by passive diffusion, showing a linear relationship between high concentrations and transport across the intestine.

3. The duodenum and upper small intestine are the sites of maximal absorption in rats and man.

4. It is estimated (but not measured) that the concentration of thiamine in the upper intestine of man is usually less than 2 µM (Hoyumpa et al, 1975).



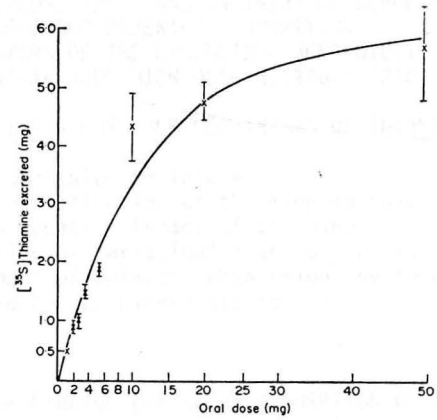
Duodenal absorption of thiamine in vivo.

From Hoyumpa et al, 1975

B. STUDIES IN MAN

In contrast to the animal studies, the studies of Thomson and Leevy (1972) suggest that in man the intestinal absorption of thiamine at doses from one to 50 mg is rate-limited. Thiamine in man appears to be absorbed by a saturable mechanism. The data are consistent with the thesis that the number of effector sites may be reduced by malnutrition.

RELATIONSHIP BETWEEN ORAL DOSE OF THIAMINE AND AMOUNT ABSORBED



Relationship between the dose of radioactive thiamine given orally and the cumulative 72 h urine radioactivity. Each point represents a mean value and the standard error is indicated. 200 mg of non-radioactive thiamine hydrochloride was given intravenously with each oral dose.

From Thomson & Leevy, 1972

THE HIGHER THE ORAL DOSE ADMINISTERED TO HUMAN SUBJECTS THE SMALLER THE PERCENTAGE ABSORBED

ORAL DOSE MG	PERCENT ABSORBED	TOTAL ABSORBED MG
1	51.0	0.5
5	35.5	1.8
20	23.8	4.8
50	11.3	5.6

From Thomson & Leevy, 1972

The mean calculated maximum amount of thiamine absorbed after a single oral dose is 8.3 $\pm$ 2.4 mg in healthy subjects and in well-nourished alcoholics (Thomson & Leevy, 1972). This is of the same order of magnitude as that noted by Friedemann et al in 1948. They reported a maximum absorption of only 14 mg per day when 40 mg was given in 3 or 4 divided doses each day.

VI. CONDITIONS ASSOCIATED WITH WERNICKE'S ENCEPHALOPATHY

1. CHRONIC ALCOHOLISM
2. MALNUTRITION FROM ANY CAUSE
3. PERSISTENT VOMITING:
   - Hyperemesis Gravidarum
   - Pyloric Stenosis
   - Cancer of the Stomach
   - Gastric Plication and Gastroplasty
4. FOOD FADDISM
5. REFEEDING AFTER PROLONGED STARVATION
6. GLUCOSE INFUSIONS IN THIAMINE DEPLETED PATIENTS
7. PROLONGED PARENTERAL NUTRITION
8. TUMORS OF THE LYMPHOID - HEMOPOIETIC SYSTEM
9. INTRAVENOUS HIGH DOSE NITROGLYCERIN

1. CHRONIC ALCOHOLISM - POSSIBLE MECHANISMS OF THIAMINE DEFICIENCY

a. Inadequate thiamine intake
b. Decreased activation of thiamine to thiamine pyrophosphate
c. Reduced hepatic storage of thiamine
d. inhibition of intestinal transport of thiamine by alcohol
e. Impairment of thiamine absorption due to ethanol related nutritional deficiency states

From Hoyumpa 1980

EFFECTS OF ETHANOL per se ON ABSORPTION OF THIAMINE

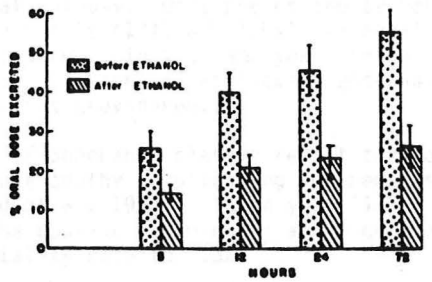


Fig. 1. The radioactivity in the serum and urine after administration of 5.0 mg. of radioactive thiamine orally to 3 healthy subjects with (- - ● - -) and without (— x —) prior administration of ethanol (1.5 Gm. per kilogram); 200 mg. of nonradioactive thiamine was given intravenously along with the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

from Thomson, Baker and Leevy, 1970

In one third of normal subjects alcohol given parenterally or orally caused a 50 percent reduction in thiamine absorption.

2. MALNUTRITION - Aside from a decreased dietary intake of thiamine, chronic malnutrition reduces intestinal absorption of thiamine by about 50 percent. Thus, when the need to absorb whatever thiamine is present in the diet is highest, the absorptive ability is greatly reduced. Several weeks of a nutritious diet reverses this process and absorptive ability returns to normal.

EFFECTS OF CHRONIC MALNUTRITION ON THE ORAL ABSORPTION OF THIAMINE. REVERSIBILITY BY 6-8 WEEKS OF A NUTRITIOUS DIET

SUBJECT	PERCENT ABSORBED
NORMALS	33.0
MALNOURISHED ALCOHOLICS	
UNTREATED	14.6
TREATED	39.4

From Thomson & Leevy, 1972

3. PERSISTENT VOMITING

A. HYPEREMESIS GRAVIDARUM

In the late 1930's and in the early 1940's the association of hyperemesis gravidarum with Wernicke's encephalopathy was well known. In 1945 King & Ride reported 371 cases of Beriberi complicating pregnancy.

In 1939 Campbell and Biggart reported 12 cases of Wernicke's encephalopathy at autopsy. Only one of the 12 patients was an alcoholic. In two patients (17%) Wernicke's encephalopathy complicated hyperemesis gravidarum. In the same year Sheehan described the typical hemorrhagic lesions of Wernicke's encephalopathy in patients dying of hyperemesis gravidarum.

At the time of Sheehan's classic report the mortality rate from Wernicke's encephalopathy complicating hyperemesis gravidarum was around 35% (Wood et al, 1983). Three years later McCoogon (1942) reported that the routine vitamin (B_1 and B complex) supplementation reduced the mortality rate to 7.3%.

It seems that each generation or two must relearn the errors of the past. In 1974 Ebels reported on the underlying illnesses of 22 patients in whom a diagnosis of Wernicke's encephalopathy was made at necropsy. Two observations are pertinent. First, 3 of the 21 cases (14%) died of Wernicke's encephalopathy precipitated by hyperemesis gravidarum. Second, Wernicke's encephalopathy is frequently overlooked in non-alcoholic patients. In only one of the 22 patients was the correct clinical diagnosis of Wernicke's encephalopathy made during life.

Cases of Wernicke's encephalopathy

Sex	Age (years)	Underlying illness
m	38	chronic alcoholism
m	40	chronic alcoholism
m	44	chronic alcoholism
m	78	chronic alcoholism; also metastasizing oat-celled carcinoma of the lung
f	33	hyperemesis of pregnancy
f	21	hyperemesis of pregnancy
f	21	hyperemesis of pregnancy
f	18	partial (criminal) abortion; hydatidiform mole
f	25	choriocarcinoma with widespread metastases
m	65	carcinoma of the stomach
f	58	carcinoma of the oesophagus
m	37	Billroth II operation for peptic ulcers
f	57	recovering from acute pancreatitis
m	72	? (vague abdominal complaints without relevant pathological findings)
m	65	? (adynamic ileus for which no cause was found)
m	30	haemodialysis in focal glomerulonephritis
m	28	retroperitoneal tumour: embryonal cell-carcinoma (primary??)
m	49	oat-celled carcinoma of the lung with widespread metastases
m	42	tumour of the base of the skull (olfactory neuroblastoma?)
m	56	purulent meningoventriculitis after heavy trauma of the skull
m	60	? (left-sided hemiatrophy of the brain; recent thrombus of the right middle cerebral artery)
f	38	? (epilepsy; ulegyria)

From Ebels, 1974

It is well known that thiamine requirements are increased during pregnancy. Recent nutritional surveys in 300 pregnant women in Los Angeles (Jacobs et al 1976) and in 599 pregnant women in Tubingen, West Germany (Heller et al 1974) have revealed a significant number patients with biochemical evidence of thiamine deficiency (22% and 26% respectively).

THIAMINE STATUS IN PREGNANCY

Week of pregnancy	Uncomplicated pregnancies				Complicated pregnancies			
	normal	marginal	deficient	marginal + deficient	normal	marginal	deficient	marginal + deficient
≤6	100 (2)	0	0	0	100.0 (1)	0	0	0
7-12	80.5 (33)	4.9 (2)	14.6 (6)	19.5 (8)	88.9 (8)	0	11.1 (1)	11.1 (1)
13-18	72.2 (39)	13.0 (7)	14.8 (8)	27.8 (15)	75.0 (3)	25.0 (1)	0	25.0 (1)
19 24	76.7 (46)	6.7 (4)	16.7 (10)	23.3 (14)	66.7 (4)	0	33.3 (2)	33.3 (2)
25-30	69.6 (55)	11.4 (9)	19.0 (15)	30.4 (24)	87.5 (7)	0	12.5 (1)	12.5 (1)
31-36	73.1 (125)	11.7 (20)	15.2 (26)	26.9 (46)	75.0 (9)	16.7 (2)	8.3 (1)	25.0 (3)
≥37	74.5 (111)	7.4 (11)	18.1 (27)	25.5 (38)	66.7 (2)	33.3 (1)	0	33.3 (1)
Total	73.9 (411)	9.5 (53)	16.6 (92)	26.1 (145)	79.1 (34)	9.3 (4)	11.6 (5)	20.9 (9)

From Heller et al, 1974

Hyperemesis superimposed on such a background can rapidly lead to Wernicke's encephalopathy during fluid and electrolyte re-replacement unless intravenous thiamine is administered.

In 1982 and 1983 four articles were published describing 7 cases of hyperemesis gravidarum complicated by Wernicke's encephalopathy. In two patients the signs and symptoms of Wernicke's encephalopathy were present on admission to the hospital. In the other five, the condition was iatrogenic in part, since it was precipitated by intravenous glucose without thiamine. One of the seven patients died and several had unfortunate neurological sequalae (Lavin et al, 1983: Watanabe et al, 1983)

B. GASTRIC PLICATION

Between 1982 and 1984, five articles were published reporting 8 patients who developed Wernicke's encephalopathy secondary to persistent vomiting following gastric plication for the control of obesity.

All of the patients had some clinical evidence of Wernicke's encephalopathy on admission. One patient was admitted with many of the classic features of Wernicke's encephalopathy but unfortunately, the condition was not recognized clinically and fatal hypotension and coma were precipitated by I.V. glucose without vitamin supplementation. In two additional instances the diagnosis was not made and serious neurological complication followed the intravenous administration of dextrose without thiamine.

It is worth noting that in three of the eight subjects photophobia was a very early symptom of Wernicke's encephalopathy. De Wardener and Lennox, (1947) reported that the photophobia occured in 6% of their subjects and at times preceded the other symptoms by as much as two weeks.

4. PROLONGED PARENTERAL NUTRITION AND SHORT-TERM I.V. GLUCOSE

The chronic malnourished patient with depleted body stores of thiamine but without clinical evidence of beriberi can experience the precipitous development of fulminant cerebral or cardiovascular beriberi by the short term administration of intravenous dextrose without thiamine supplementation (Watson et al, 1981/Drenick et al, 1966).

Recently, Shorey et al (1984), reported the sudden onset of acute Wernicke's encephalopathy in a non-alcoholic patient 48 hours following continuous administration of high-dose intravenous nitroglycerin for unstable angina. The intravenous nitroglycerin formulation contained large amounts of ethanol and glucose.

In view of the paucity of body stores of thiamine even in well nourished subjects Wernicke's encephalopathy can appear after 9 to 27 days of thiamine deprivation. Long-term parenteral therapy with glucose containing solutions should predictably produce beriberi in some previously well nourished subjects.

Within the period between 1975 and 1980 nine articles were published reporting the precipitation of Wernicke's encephalopathy in 14 patients following prolonged parenteral therapy. The condition was frequently not diagnosed and 8 of the 14 patients died (57%). In 5 of the eight patients who died, the major clinical manifestations of Wernicke's encephalopathy were coma $\pm$ hypotension and hypothermia.

Literature Review: Wernicke's encephalopathy following prolonged intravenous therapy

Author	Age	Sex	Presenting medical condition	Therapy	Onset* (days)	Clinical signs and symptoms	Outcome	Pathology
Blennow, 1975[3]	14	M	Esophageal achalasia rupture following dilatation	IV fluids	28	Somnolence, nystagmus VI cranial nerve palsies	Given thiamine-recovered	
Nadel and Burger 1976[4]	78	F	Hyperparathyroidism	IV fluids 5% dextrose 0.45% saline	56	Coma	Died	Hemorrhages in periventricular regions and MB
	61	F	Parathyroid adenoma Post-op nausea and vomiting	IV fluids 5% dextrose, albumin and saline	20	Sudden coma, hypotension	Died	Hemorrhages in MB
Baugham and Papp 1976[5]	61	F	Persistent vomiting with weight loss	IV fluids 5% Aminosol Multivitamins	19	Numbness, dysarthria ataxia	Given thiamine-recovered	
Kramer and Goodwin 1977[6]	63	F	Minor head injury perforated viscus	IV fluids dextrose Intralipid	27	Disorientated, gaze palsies, nystagmus, ataxia	Given thiamine-recovered	
Lowdale, 1978	57	F	Esophagitis and gastritis with bleeding	IV fluids 5% dextrose, blood Multivitamins	80	Anxiety, lethargy, obtundation	Died	Early Wernicke's encephalopathy
Harper[1]	50	M	Ischio-rectal abscess	IV fluids 50% dextrose and insulin	12	Post-op coma and hypotension	Died	Hemorrhages in periventricular regions and MB
	71	M	Small bowel obstruction	IV fluids 5% dextrose 0.45% saline Multivitamins	4	Coma, hypotension, hypothermia	Died	Hemorrhages in periventricular regions and MB
	68	M	Acute pancreatitis	IV fluids 50% dextrose Multivitamins	40	Coma, hypotension	Died	Hemorrhages in periventricular regions and MB

*Onset of clinical symptoms after admission

From Harper, 1980

IN THE LAST NINE YEARS 30 CASES OF COMA AS THE PREDOMINANT FEATURE IN WERNICKE'S ENCEPHALOPATHY HAVE BEEN REPORTED. Analysis of these cases reveals that hypothermia and hypotension frequently accompany the coma. It is important to remember that in 1947 DeWardener & Lennox reported that in 19% of their cases of Wernicke's encephalopathy the sudden onset of advanced mental changes was the first evidence of this disorder.

In patients with coma, with or without hypotension or hypothermia, the overall mortality rate was 35% in the thiamine treated cases and 100% in untreated cases.

5. TUMORS OF THE LYMPHOID - HEMOPOIETIC SYSTEMS

In 1981 J. DeReuck, Coster and Vander Eecken reported that in a prospective neuropathologic study, Wernicke's encephalopathy was the most frequent intracranial complication of treated patients with tumors of the lymphoid-hematopoietic systems. The highest incidence was found in elderly patients and in patients with prolonged survival.

INCIDENCE OF INTRACRANIAL COMPLICATIONS IN 24 BRAINS OF PATIENTS WITH LYMPHOID-HEMOPOIETIC TUMORS (De Reuck, 1980)

WERNICKE'S ENCEPHALOPATHY	8
LEUKEMIC INVASION	6
HEMORRHAGE	5
ABSCESS	3
CALCIFICATIONS	1

VII CLINICAL PICTURE OF WERNICKE'S ENCEPHALOPATHY

A. THE SIGNS OF WERNICKE'S ENCEPHALOPATHY REPORTED IN TWO LARGE SERIES

	Victor, Adams & Collins (1971) (>200 Cases)	DeWardener & Lennox (1947) (52 Cases)
EYE CHANGES	96%	100%
Nystagmus	85%	100%
Lateral Rectus Palsy	54%	26%
Conjugate Gaze Palsy	44%	8%
Pupillary Changes	19%	4%
Ptosis	3%	2%
MENTAL CHANGES	90%	78%
Global Confusional State	56%	57%
Disorder of Memory	57%	61%
Delirium Tremens	16%	-0-
ATAXIA	87%	4%
Of Gait	87%	
Of Legs	20%	
Of Arms	12%	

B. THE CLINICAL PICTURE OF CEREBRAL BERIBERI IN 52 NON-ALCOHOLICS SIGNS AND SYMPTOMS IN ORDER OF APPEARANCE (DeWardener & Lennox, 1947)

1. PERSISTENT ANOREXIA - Followed in about 1 week by vomiting

2. VOMITING - Not always with meals, often on awakening, usually 4-5 times a day. Violent when associated with dizziness

3. NYSTAGMUS - Starts a few days after vomiting horizontal more often than vertical

4. PROGRESSIVE MENTAL DETERIORATION
   a. Loss of interest in past and then present
   b. Miserable inactivity
   c. Sleepless, disoriented, uncooperative

5. TERMINALLY - Semi-coma and severe oculumotor palsies

6. SUDDEN ONSET OF ADVANCED MENTAL CHANGES is the first evidence for Wernicke's encephalopathy in 19 percent of patients

C. EARLIEST SYMPTOMS & SIGNS OF WERNICKE'S ENCEPHALOPATHY

The studies of Williams et al (1940, 1943) in experimental thiamine deficiency give clear evidence that various combinations of fatigue, listlessness, inactivity, persistent and worsening nausea, insomnia, mental depression, apathy, loss of interest in the past and present associated with protracted vomiting precede the development of nystagmus, ophthalmoplegias, global confusional state and ataxia. Moreover, these early symptoms and signs disappear within a few hours after parenteral thiamine therapy.

VIII FAILURE TO APPROPRIATELY DIAGNOSE WERNICKE'S ENCEPHALOPATHY ON THE BASIS OF THE ABOVE CRITERIA

Typical lesions of Wernicke's encephalopathy are often found at necropsy in patients clinically undiagnosed because of the absence of the "classical clinical features" (Grunnet, 1969). The clinical hetergeneity of Wernicke's encephalopathy results in the condition remaining undetected if the classical symptoms and signs are awaited before the diagnosis is made.

COMPARISON OF THE INCIDENCE OF WERNICKE'S ENCEPHALOPATHY DIAGNOSED DURING HOSPITALIZATION VS AUTOSPY RATE

INCIDENCE - ALL HOSPITAL ADMISSIONS	RATE PER 10,000	PERCENT
AT MASSACHUSETTS GENERAL HOSPITAL	5	0.05
AT BOSTON CITY HOSPITAL	13	0.13
AT ROYAL PERTH HOSPITAL	4	0.04
INCIDENCE - HOSPITAL AUTOPSY RATES		
IN USA	200	2.0
IN AUSTRALIA	200	2.0

FREQUENCY OF CORRECT CLINICAL DIAGNOSIS IN PATIENTS FOUND AT AUTOPSY WITH WERNICKE'S ENCEPHALOPATHY

Author	Number of Autopsy Cases of W E	Seen At Univ. Hosp.	Correct Clinical Diagnosis
Ebels 1974	22	yes	4.5%
Torvik 1982 & 85	40	yes	2.5%
Harper 1979	51	yes	14.0%
1983		yes	20.0%

IX SUMMARY THOUGHTS ABOUT THE CLINICAL PICTURE OF WERNICKE'S ENCEPHALOPATHY (W-E)

The clinical heterogeneity seen in W-E should not be surprising but even expected on the basis not only of the diverse pathological involvement but also on the frequency and severity of repeated episodes of thiamine deficiency experienced by patients.

In Wernicke's encephalopathy the neuropathologic changes which are specific for this disease include necrosis of nerve cells and myelinated structures. These lesions are distributed in a bilaterally symmetrical fashion and involve in different combinations the mammillary bodies, the superior cerebellar vermis, the hypothalamic nuclei, the third and sixth nerve nuclei, the tegmentum, the vestibular nuclei, the thalamus, the midbrain, the pons and the medulla. The variable involvement produces a diverse clinical picture.

We therefore should neither wait for nor expect the combination of the "classical" symptoms of global confusion, eye signs and ataxia before the diagnosis is made.

Any sick malnourished patient, alcoholic and non-alcoholic, or one with a history of inadequate thiamine intake, even in the absence of any of the diverse clinical signs or symptoms of Wernicke's encephalopathy should receive prophylactic intravenous or intramuscular thiamine especially if the administration of intravenous fluids containing glucose is contemplated.

WERNICKE'S ENCEPHALOPATHY SHOULD BE SUSPECTED AT THE BEDSIDE AND TREATED IN ANY PATIENT WITH ANY COMBINATION OF THE FOLLOWING SIGNS AND SYMPTOMS, EXPECIALLY IF THE HISTORY SUGGESTS THE POSSIBLITY OF DIETARY DEFICIENCY OF THIAMINE.

SIGNS AND SYMPTOMS OF WERNICKE'S ENCEPHALOPATHY

GENERAL

Loss of appetite		Hypothermia
Nausea and persistent vomiting		Hypotension
Insomnia, Fatigue & Lassitude		

EYE

Diplopia	Nystagmus	Ptosis
Jumping of eyes	Oscillopsia	Scotomata
Photophobia	Lateral Rectus Palsy	Pupillary Changes
Wavering of eye fields	Conjugate Gaze Palsy	

MENTAL STATE

Apprehension	Stupor	Global Confusion
Apathy	Coma	Disorder of Memory
Excitement	Hallucinations	Withdrawal Syndrome
Disorentation	Convulsions	

BALANCE AND GAIT

Unsteadiness	Ataxia of Gait
Dizziness	Ataxia of Extremities
Vertigo	Ataxia of Speech

X RECENT EVIDENCE FOR A GENETIC PREDISPOSITON TO DEVELOPE WERNICKE'S ENCEPHALOPATHY

The fact that only a small percent of malnourished alcoholics and that only a small minority of normal people subjected to thiamine deprivation develope Wernicke's encephalopathy has raised the possibility of a genetic predisposition in certain patients.

Whether or not Wernicke-Korsakoff syndrome occurs randomly throughout the population or only in particular subset of those at risk has received a great deal of recent attention.

To what extent inborn errors of metabolism predispose individuals who abuse alcohol to the development of specific complications of alcoholism has received attention over many years (Omen & Motulsky, 1972). Recent evidence for a genetic susceptibility to the Wernicke-Korsakoff syndrome will be reviewed.

A. GENETIC VARIATION IN TRANSKETOLASE

In 1977 Blass & Gibson reported studies indicating that in the cultured fibroblasts of four patients with Wernicke-Korsakoff syndrome an abnormal transketolase enzyme was found which had a much higher Km for thiamine pyrophosphate than six control subjects. The activity of the transketolase enzyme in these patients and controls was not different.

They postulated that this abnormality of transketolase might not be clinically important if the diet contained ample amounts of thiamine but would have a deleterious effect when the diet was inadequate and plasma levels of thiamine fell.

ACTIVITY OF TRANSKETOLASE IN PATIENT AND CONTROL CELLS

ACTIVITIES

nmol/min/mg of protein

Patients		Controls	
Case 1	15 ± 3	No. 1	18,20
Case 2	22 ± 4	No. 2	19 ± 3
Case 3	24 ± 1	No. 3	16 ± 3
Case 4	27 ± 5	No. 4	21 ± 3
		No. 5	16 ± 3
Mean	22 ± 3	No. 6	19 ± 1
		No. 7	12,14
		No. 8	11,15
		No. 9	19,19
		No. 10	19 ± 3
		Mean	17 ± 1

From Blass & Gibson, 1977

Km VALUES FOR THIAMINE PHYROPHOSPHATE FOR TRANSKETOLASE FROM PATIENTS AND CONTROLS

	Km For TPP (μM)		
	Patients		Controls
Case 1	281 ± 79	No. 1	20 ± 9
Case 2	196 ± 45	No. 2	20 ± 4
Case 3	156 ± 40	No. 3	15 ± 5
Case 4	146 ± 45	No. 4	15 ± 5
		No. 5	12 ± 3
Mean	195 ± 31	No. 6	11 ± 3
		Mean	16 ± 2

From Blass & Gibson, 1977

RECENTLY, NIXON AND COLLEAGUES (1984) AT THE UNIVERSITY OF QUEENSLAND REPORTED EXCITING NEW STUDIES BEARING ON THE POSSIBILITY OF A GENETIC LINK TO THE DEVELOPMENT OF WERNICKE-KORSAKOFF SYNDROME IN A SUBSET OF THE POPULATION

FIRST, they were unable to confirm the studies of Blass & Gibson (1977). The apparent Km for RBC transketolase in 23 healthy subjects, 7 chronic alcoholics and 53 subjects with Wernicke's encephalopathy were not significantly different.

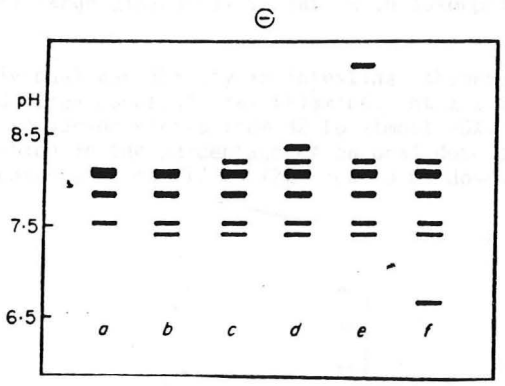
APPARENT K_m VALUES OF ERYHROCYTE TRANSKETOLASE FOR TDP

SUBJECTS	NUMBER OF SUBJECTS	PREFORMED HOLO-TRANSKETOLASE (MEAN $K_m \pm 2$ SD) ($NMOL\ L^{-1}$)	IMMEDIATE ASSAY ALL REAGENTS ADDED TOGETHER (MEAN $K_m \pm 2$ SD) ($\mu MOL\ L^{-1}$)
HEALTHY CONTROLS	23	54 ± 18	2.4 ± 2.4
ALCOHOLIC CONTROLS	7	64 ± 18	2.3 ± 1.6
PATIENTS WITH KORSAKOFF'S PSYCHOSIS AND DEFINITE WERNICKE'S ENCEPHALOPATHY	17	64 ± 32	2.2 ± 2.4
PROBABLE WERNICKE'S ENCEPHALOPATHY	27	69 ± 24	1.8 ± 2.0
POSSIBLE WERNICKE'S ENCEPHALOPATHY	9	70 ± 16	1.8 ± 1.6

Nixon et al, 1984

SECOND, by isoelectric focussing they separated erythrocyte transketolase into 8 different isoenzymes with pI values ranging from 6.6 - 9.2. Six distinct patterns of isoenzymes were found in 36 healthy control subjects.

DIAGRAM OF THE PATTERNS OF TRANSKETOLASE ISOENZYMES SEPARABLE BY ISOELECTRIC FOCUSSING. EACH ERYTHROCYTE LYSATE YIELDED ONE OF THE PATTERNS LABELLED a-f



From Nixon et al, 1984

THIRD, the isoenzyme pattern for 39 of the 42 patients with Wernicke-Korsakoff syndrome (93%) was indentical to a pattern found in only 8 of 36 control subjects (22%).

DISTRIBUTION OF ISOENZYME PATTERNS FOR TRANSKETOLASE FROM HUMAN ERYTHROCYTES

SUBJECTS	PATTERNS a	b	c	d	e	f
HEALTHY CONTROLS	3	15	8	7	2	1
ALCOHOLIC CONTROLS	0	6	0	0	0	0
PATIENTS WITH KORSAKOFF'S PSYCHOSIS AND DEFINITE WERNICKE'S ENCEPHALOPATHY	0	0	13	1	0	0
PROBABLE WERNICKE's ENCEPHALOPATHY	0	1	18	0	0	0
POSSIBLE WERNICKE'S ENCEPHALOPATHY	0	0	8	1	0	0

NIXON et al 1984

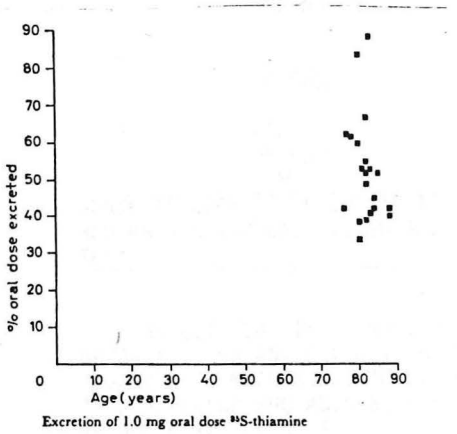
The highly significant association between erythrocyte transketolase isoenzyme pattern c and patients suffering from W-K syndrome suggest that THIAMINE DEFICIENCY and this VARIANT TRANSKETOLASE contribute to the pathogenesis of the characteristic brain damage in the Wernicke-Korsakoff syndrome by some mechanism independent of apparent K_m values of transketolase for thiamine diphosphate.

B. BIOLOGIC (GENETIC?) VARIABILITY IN THIAMINE ABSORPTION

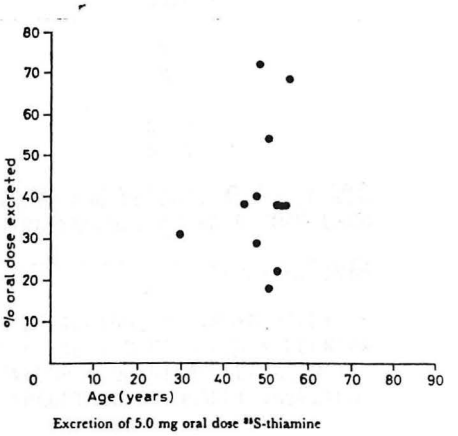
There is evidence suggesting that a subset of the population is hypersusceptible to the development of thiamine deficiency as a consequence of a biologically determined limited capacity to absorb thiamine.

Although the studies on absorption show great reproducibility, there is very large biological variation in absorption from person to person.

The individual variability in intestinal absorption is present at small and large doses of oral thiamine. At a 1 mg dose absorption from person to person varies from 32 to almost 90%. Large person to person variation in the percentage of an oral dose absorbed also is present at doses of 5 mg (17 to 72%) and 20 mg doses (8 to 54%).



Excretion of 1.0 mg oral dose ^{35}S-thiamine



Excretion of 5.0 mg oral dose ^{35}S-thiamine

(From Thomson, 1966)

MOST IMPORTANT IS THE FACT THAT BOTH THOSE INDIVIDUALS WHO ABSORB A HIGH PERCENTAGE OF AN ORAL THIAMINE AND THOSE PERSONS WHO ABSORB A LOW PERCENTAGE DO THIS CONSISTENTLY ON REPEATED TESTING.

REPRODUCTABILITY OF THIAMINE ABSORPTION IN INDIVIDUAL SUBJECTS

SUBJECT	TEST	[^{35}S]THIAMINE URINARY EXCRETION (%)
1	FIRST	49.0
	SECOND	53.0
2	FIRST	49.0
	SECOND	49.0
3	FIRST	41.7
	SECOND	41.2
4	FIRST	75.0
	SECOND	80.0
5	FIRST	58.5
	SECOND	58.0
6	FIRST	59.9
	SECOND	59.0

SUBJECTS WERE GIVEN TWO TESTS: FIRST* AND SECOND† AND RECEIVED 300 MG NON-RADIOACTIVE THIAMINE INTRAVENOUSLY 48 HR BEFORE EACH TEST.

Thomsom, 1966

THE CLINICAL IMPORTANCE OF THESE FINDINGS IS IMMEDIATELY APPARENT. ON ANY GIVEN THIAMINE DEFICIENT DIET A LOW PERCENTAGE ABSORBER IS MUCH MORE LIKELY TO DEVELOP A CLINICAL DEFICIENCY THAN A PERSON WHO ABSORBS A HIGH PERCENTAGE OF ORALLY INGESTED THIAMINE IN THE DIET.

XI. COURSE OF WERNICKE'S ENCEPHALOPATHY

MORTALITY - After clinical diagnosis was made, 17% died during the acute illness. The mortality rate is grossly underestimated in view of the fact that autopsy diagnosed cases frequently are unrecognized clinically.

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 Change

MENTAL CHANGES

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

84% of WERNICKE'S Developed KORSAKOFF'S PSYCHOSIS (Victor, 1971)
Complete Recovery in only 21%
Moderate Improvement in 25%
No Significant Improvement in 54%

XII GUIDELINES IN THE TREATMENT OF WERNICKE-KORSAKOFF'S SYNDROME

Since Wernicke's encephalopathy is a potentially reversible disorder if treatment is instituted immediately whereas death or severe neurological sequelae are the consequence of late treatment, this disorder must be viewed as a medical emergency.

Prophylactic treatment in any malnourished patient who has a history of poor dietary intake is mandatory especially if intravenous dextrose is to be administered for short or long term.

Every chronic alcoholic should receive prophylactic treatment since Wernicke's encephalopathy may be precipitated by a few liters of intravenous fluids containing glucose.

Thiamine should initially be administered daily by the intravenous route in doses of at least 100 mg along with therapeutic doses of B complex. Thereafter 100 mg, plus B complex should be administered either intravenously or intramuscularly on a daily basis.

Do not depend on oral thiamine therapy since malnutrition seriously decreases thiamine absorption and those patients who are poor absorbers of thiamine are the ones most likely to develop the deficiency state.

Hypomagnesemia and hypophosphatemia must be treated at once since both are essential for the phosphorylation of thiamine to the coenzyme thiamine pyrophosphate. Additionally, there is evidence indicating that either transketolase apoenzyme production may be diminished or the joining of the coenzyme to the apoenzyme decreased in magnesium depletion.

IT IS MOST IMPORTANT TO BE CONSTANTLY ALERT TO THE POSSIBILITY OF THIAMINE DEPRIVATION IN ANY SICK PATIENT WHERE CLINICAL FINDINGS OR HISTORY SUGGEST THIS DEFICIENCY AND THEN TO TREAT AT ONCE WITH LARGE DOSES OF INTRAVENOUS THIAMINE AND B-COMPLEX.

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