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Research Article

URINARY EXCRETION OF THIAMIN IN CLINICAL CASES AND THE VALUE OF SUCH ANALYSES IN THE DIAGNOSIS OF THIAMIN DEFICIENCY [1]

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An accurate and specific method for the determination of thiamin in urine, based on the reaction between the vitamin and diazotized p-aminoacetophenone, has been developed (1). Under suitable conditions, such determinations should give information regarding the state of saturation of an organism with this vitamin. Studies of the urinary excretion of thiamin in normal subjects before and after test doses, the factors influencing such excretion, and the changes associated with experimental deficiency have been reported (2). The present communication deals with determinations of the urinary excretion of thiamin in 89 patients in the University Hospital, correlation of these values with dietary histories of these patients, and the evaluation of the possible association of thiamin deficiency with the clinical conditions encountered.

CONDITIONS AND METHODS

The thiamin content of the diet ingested by each patient during the month prior to the test was evaluated on the basis of repeatedly consistent details of the dietary history as obtained by more than one questioner. This was classified as deficient only when obviously so, as suboptimal when the diet was low in protective foods but not grossly deficient, and as adequate when estimations indicated an intake of two-thirds of a milligram (220 international units), or more.

Two consecutive 24-hour urine specimens were collected from each patient. Just prior to the beginning of the second sample and after the largest meal of the day, an aqueous solution of 5 mgm. of thiamin was taken orally. Previous studies (2) indicate the advisability of using the oral route for the test dose and the necessity of giving it with a meal. The first sample was analyzed to give the 24-hour excretion value when the diet furnished the entire supply of the vitamin. As the patients ate the same diet on the 2 consecutive days, the value for the first sample was subtracted from the value obtained by analysis of the second sample in order to calculate the percentage of the test dose excreted in the 24 hours following its administration. The method of analysis has been described in detail elsewhere (1).

Since drastic reduction of the dietary thiamin of normal subjects resulted in a rapid decrease of urinary thiamin excretion (2), the thiamin content of the diets ingested on the days of the tests is estimated in the tables. When numerical values are given, calculations are based on the tables compiled by Williams and Spies (3). Unless otherwise indicated, the tests were done before the fifth day of hospitalization. The absence of an appreciable increase in the urinary excretion during the first few days after resumption of a normal thiamin intake by a subject with experimental deficiency (2) demonstrates that the ingestion of an adequate diet by the deficient individual for a few days prior to the test does not vitiate the significance of subsequent values.

RESULTS

Standards. Standards for the interpretation of values obtained, with chief attention directed to the minimal normal excretion of thiamin, have been derived by correlating the urinary thiamin values for each subject with the adequacy of the dietary thiamin intake during the preceding month in a series of 24 normal controls (2), 22 hospital patients without clinical evidence of nutritional

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[2] Upjohn Fellow in Clinical Research, 1938–1940.

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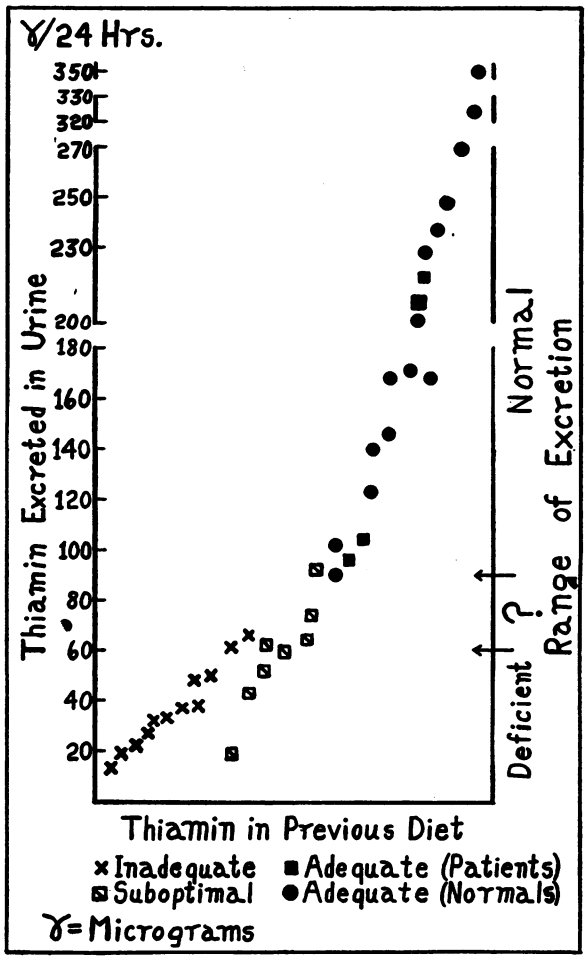

FIG. 1. CORRELATION IN ADULT MALES BETWEEN THE ADEQUACY OF THE PRECEDING DIETARY THIAMIN INTAKE AND THE 24-HOUR URINARY THIAMIN EXCRETION

deficiencies, and 24 patients with clinical evidence of deficiencies in one or more nutritional factors, including 3 patients with "alcoholic beriberi." All patients were excluded who had disorders which might lead to faulty absorption, storage, utilization or excretion of the vitamin.

Figure 1 presents the values of urinary thiamin excretion by male subjects during the time that the diet furnished the entire source of thiamin. Those whose preceding diets had been definitely inadequate excreted 66 micrograms or less per 24 hours, whereas all subjects who had previously been on adequate diets excreted 90 micrograms or more. With the female subjects (Figure 2) the division is not so sharp, but no subject who had taken an adequate thiamin intake excreted less than 53 micrograms per 24 hours and only 1 excreted less than 60 micrograms. Only 1 female with a history of a definitely inadequate diet excreted more than 43 micrograms. Since no significant difference was seen between males and females in the per cent of the oral dose excreted, these data for both sexes are presented in Figure 3. All patients with a history of a preceding inadequate thiamin intake excreted less than 7 per cent of the oral dose; all 27 subjects whose diets had been adequate excreted about 8 per cent or more, and 22 of the 27 excreted 10 per cent or more.

It appears that if a male subject fails to excrete more than 90 micrograms of thiamin during a 24-hour period when he is ingesting an adequate diet, he may be suspected of having a significant reduction of the body stores of thiamin, and if he excretes less than 60 micrograms, such reduction is reasonably certain. Corresponding values for females place the lower limit of normal excretion at 60 micrograms, with values below 40 micrograms

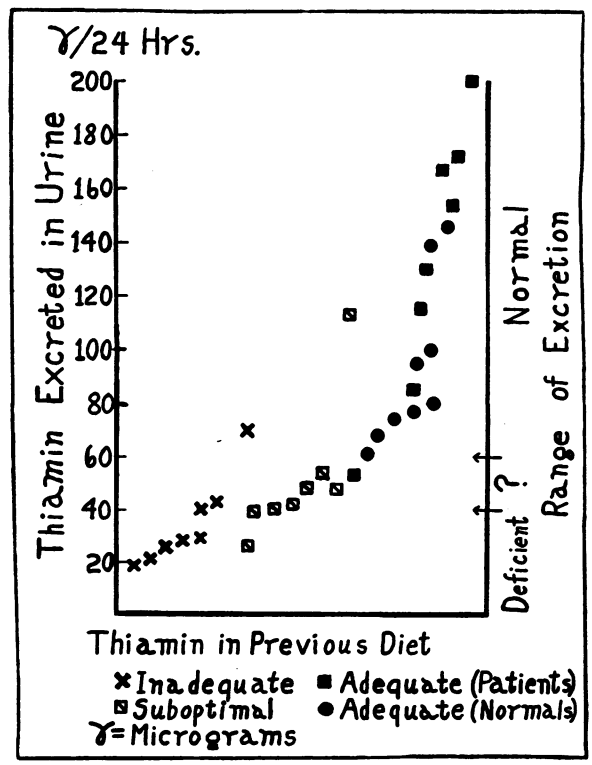

FIG. 2. CORRELATION IN ADULT FEMALES BETWEEN THE ADEQUACY OF THE PRECEDING DIETARY THIAMIN INTAKE AND THE 24-HOUR URINARY THIAMIN EXCRETION

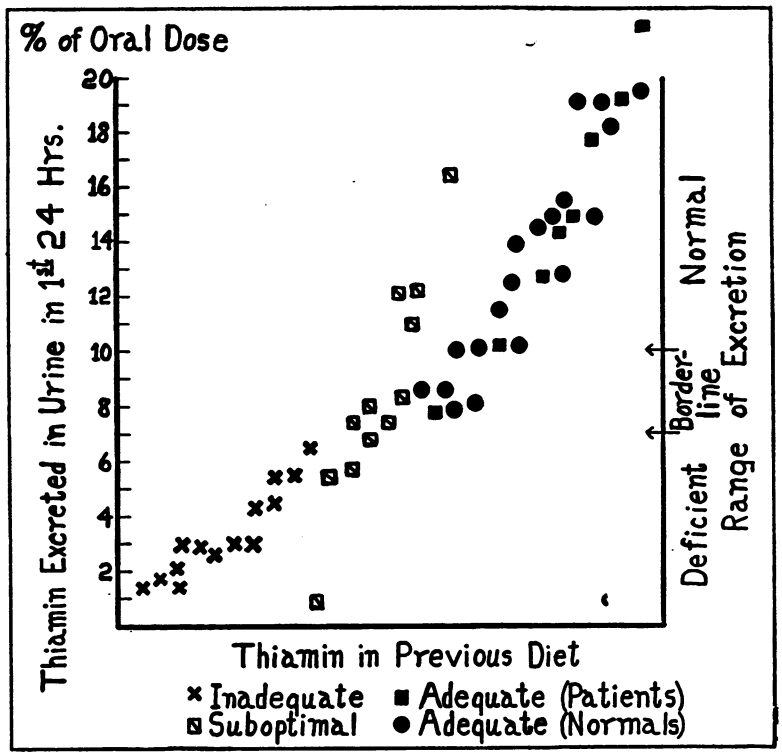

FIG. 3. CORRELATION IN ADULT MALES AND FEMALES BETWEEN THE ADEQUACY OF THE PRECEDING DIETARY THIAMIN INTAKE AND THE PERCENTAGE OF A 5 MGM. TEST DOSE OF THIAMIN EXCRETED IN THE URINE DURING THE FIRST 24 HOURS AFTER IT IS TAKEN ORALLY WITH A MEAL

The excretion values are corrected for the amount of thiamin from dietary sources excreted during the test period.

indicative of a fairly certain depletion. Excretion by a member of either sex of less than 7 per cent of a 5 mgm. oral test dose taken with a meal is also evidence of depletion of thiamin stores. It is pertinent to note that values for the normal excretions used in estimating these standards are obtained from subjects in whom no attempt at saturation with the vitamin has been made. These minimal standards for thiamin excretion are purposely conservative.

Patients with clinical thiamin deficiency. Three patients with peripheral polyneuritis, clinically identical with that of beriberi (4), were studied. Case 1 in addition presented all the findings of "beriberi heart disease" (5). Alcoholism was responsible for a grossly inadequate dietary intake in each case. In these patients, the values for thiamin excretion, presented in Table I, are much below those of the controls, both before and after the oral dose. Each of these patients also ex-

TABLE I

Urinary excretion of thiamin by patients with clinical thiamin deficiency

Case number	Sex	Age	Clinical diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Thiamin excreted in urine		Fraction of oral dose excreted in urine
						Before oral dose	After oral dose	
		years			*micrograms per 24 hours*	*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*
1	M	36	Peripheral polyneuritis and "wet beriberi"	Inadequate	360	13	120	2.1
			Three days after cessation of treatment		360	398	1000	12.0
2	M	61	Peripheral polyneuritis*	Inadequate	530	50		
			Two days after cessation of treatment		530	240		
3	M	64	Peripheral polyneuritis	Inadequate	870	19	232	4.3

* This patient also had clinical evidence of scurvy, and a plasma ascorbic acid value of 0.17 mgm. per 100 cc.

creted definitely less thiamin in the urine after parenteral test doses than did normal subjects. All 3 patients showed excellent clinical improvement after treatment with crystalline thiamin, adequate diets, and other vitamin supplements as indicated by coincident deficiencies.

After treatment, Cases 1 and 2 returned to the diets on which the original tests were done and showed urinary excretions in the high normal range. The high urinary excretion after treatment, when no test dose was given, may be due, in part, to excess storage of the vitamin given therapeutically. Subsequent studies (2) have indicated that a longer interval is required for the urinary thiamin excretion of a normal subject to return to its basal level after discontinuation of supplementary thiamin.

TABLE II

Urinary excretion of thiamin by patients with nutritional deficiency

Case number	Sex	Age	Clinical diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Thiamin excreted in urine		Fraction of oral dose excreted in urine
						Before oral dose	After oral dose	
		years				micrograms per 24 hours	micrograms per 24 hours	per cent
4	F	40	Pellagra	Adequate	Good	167	882	14.3
5	F	19	Pellagra	Suboptimal	Fair	29	1308	25.6
6	F	33	Pellagra	Suboptimal	Fair	39	858	16.4
7	F	53	Pellagra	Suboptimal	Good	48	600	11.0
8	F	19	Pellagra, and migraine	Suboptimal	Low	42	414	7.4
9	F	38	Pellagra	Suboptimal	Fair	54		
10	F	18	Pellagra—"anorexia nervosa"*	Inadequate	Fair	43	366	6.5
11	F	44	Pellagra and psychoneurosis*	Inadequate	Low	26		†
12	F	37	Pellagra and hyperemesis gravidarum	Inadequate	Good	28	300	5.4
13	F	34	Pellagra	Inadequate	Low	18	292	5.5
14	F	47	Pellagra	Inadequate	Fair	21	170	3.0
15	F	17	Pellagra and microcytic anemia	Inadequate	Good	40	270	4.6†
			After treatment		Good	208	1765	31.1‡
16	M	29	Angular stomatitis	Suboptimal	Fair	62	666	12.1
17	M	24	Hypovitaminosis A*	Suboptimal	Low	52	660	11.0
18	M	61	Pellagra	Suboptimal	Good	92	450	7.4
19	M	57	Pellagra and bizarre gastritis	Inadequate	Fair	37	1285	25.0
20	M	61	Scurvy and pellagra*	Inadequate	Low	22		†
21	M	64	Pellagra and neoplasm of jaw	Inadequate	Good	32	180	3.0
22	M	57	Pellagra and urinary infection*	Inadequate	Good	27	176	3.0
23	M	54	Pellagra, scurvy and atrophic arthritis*	Inadequate	Good	61	146	1.7
24	M	58	Pellagra and Hodgkin's disease*	Inadequate	Fair	66	138	1.4

* These patients had plasma ascorbic acid values of less than 0.5 mgm. per 100 cc. on or shortly after admission.

† These patients also excreted during continuous intravenous administration of thiamin significantly less of the vitamin than did normal controls.

‡ After treatment, the excretion of thiamin during continuous intravenous administration was also in the range of the normal control values.

Patients with other nutritional deficiencies. Twenty-one patients who presented clinical evidence of single or multiple nutritional deficiencies as a major, and often the sole, cause of symptoms were studied. The results are presented in Table II. None of these cases presented unequivocal clinical evidence of thiamin deficiency. It should be noted that we have made the diagnosis of pellagra in patients who have manifestations other than the classical dermatitis, and that many foods with a fair to good thiamin content (3) are not highly pellagra-preventive (6). The clinical diagnosis in these cases was confirmed by observation of a significant response to therapy with appropriate vitamin supplements. All but 1 patient showed excretions before the test dose definitely lower than the values obtained on normals, and 9 of the 18 cases given the oral test dose excreted less than 7 per cent thereof. Cases 5 and 19 show apparently paradoxical values, with low excretion on the diet alone and unusually high values after the oral dose. The tests were repeated on Case 15 8 days after the cessation of treatment with a yeast and liver concentrate of high thiamin content. Values well in the normal range were obtained then.

Patients with organic heart disease. The fact that thiamin deficiency *per se* can cause serious cardiovascular disturbances (5, 7, 8) has led to consideration of the possibility that a concomitant but less evident deficiency may contribute to the clinical disability in organic heart disease (9, 10, 11). Restriction of the intake of the "protective foods" is not uncommon in chronic cardiac disease, either as a result of gastro-intestinal symptoms or as part of the therapeutic regimen. Table III presents the urinary thiamin excretion values of 7 patients who were hospitalized for treatment of cardiac decompensation. There was no evidence of impairment of renal function in these cases. Case 31, the only one to show excretions definitely in the normal range, was tested after recovery from decompensation. However, all 7 patients responded satisfactorily to the usual treatment with bed rest, digitalization and diuretics, on an adequate diet without vitamin supplements. Cases 26, 28, and 29 failed to show any additional

TABLE III

Urinary excretion of thiamin by patients with organic heart disease

Case number	Sex	Age	Type of heart disease	Degree of decompensation when tested	Thiamin content of previous diet	Dietary thiamin during test	Thiamin excreted in urine		Fraction of oral dose excreted in urine
							Before oral dose	After oral dose	
		years					*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*
25	M	50	Hypertensive	++++	Inadequate	Fair (650 γ)	33	180	2.9
26	M	54	Hypertensive	+++	Suboptimal	Fair (500 γ)	19	63	0.9
27	M	54	Coronary	+++	Suboptimal	Good (780 γ)	64	348	5.7
28	M	66	Arteriosclerotic	++	Suboptimal	Fair	74		
29	M	37	Rheumatic	+	Suboptimal	Fair	59		
30	F	52	Hypertensive	+	Suboptimal	Fair	113	384	5.4
31	M	43	Hypertensive	0	Adequate	Good (700 γ)	104	850	14.9

improvement objectively when large doses of crystalline thiamin were given.

Patients with endocrine disorders. By inference from work on experimental animals, some of the diseases of endocrine origin have been suspected of being associated with abnormalities in utilization of thiamin. Himwich and associates (12) have accelerated the appearance of vitamin B deficiency in dogs by massive doses of thyroid. Other workers (13, 14, 15, 16) have demonstrated that the amount of thiamin required to maintain weight gain in rats and pigeons is increased by experimentally-induced hyperthyroidism. Frazier and Ravdin (17) have reported improved results by the use of yeast and thiamin in the preoperative preparation of hyperthyroid patients. Table IV presents the values for thiamin excretion on 7 patients with toxic goiter, 6 of whom show values

TABLE IV

Urinary excretion of thiamin by patients with endocrine disorders

Case number	Sex	Age	Clinical diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Thiamin excreted in urine		Fraction of oral dose excreted in urine
						Before oral dose	After oral dose	
		years				*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*
32	F	36	Exophthalmic goiter	Adequate	Good	106	1206	22.0
33	F	47	Exophthalmic goiter	Adequate	Good	56	750	13.9
34	F	36	Recurrent exophthalmic goiter	Adequate	Good	157	750	11.9
35	M	35	Toxic adenomatous goiter	Adequate	Good	149	1140	19.8
36	M	34	Exophthalmic goiter	Adequate	Good	188	1026	16.8
37	M	20	Exophthalmic goiter	Adequate	Good	195	732	10.7
38	M	47	Exophthalmic goiter	Inadequate for 2½ weeks	Good (980 γ)	44	182	2.8
39	F	51	Myxedema	Suboptimal	Fair	18	230	4.2
40	F	52	Diabetes mellitus*	Adequate	Good (900 γ)	70	705	12.7
41	F	53	Diabetes mellitus*	Adequate	Good	144	846	14.0
42	F	67	Diabetes mellitus†	Adequate	Good	46	924	17.6
43	M	68	Diabetes mellitus†	Adequate	Good	127		
44	M	25	Diabetes mellitus‡	Adequate	Fair	103	690	11.7
45	M	27	Diabetes mellitus‡	Adequate	Good	300	1152	17.0

* No neurologic complaints; neurologic examination normal.
† Symptoms, sensory disturbances and reflex changes of peripheral neuritis.
‡ No symptoms or sensory disturbances. Absent tendon reflexes in lower extremities.

well within the normal range. These patients had experienced the usual polyphagia of their disease and had taken diets of high caloric and vitamin content. Case 38, who showed definitely low urinary thiamin values, had also eaten well until anorexia developed about 18 days prior to the tests. He was extremely toxic on admission and went into thyroid crisis which terminated fatally on the seventh day of hospitalization. These findings suggest that in hyperthyroidism the usual increase in food consumption suffices to meet the increased requirement for thiamin, but that in the occasional patient with poor appetite or gastro-intestinal disturbances a deficiency of this vitamin may rapidly develop. The 1 case with classical myxedema studied showed low values for thiamin excretion; this patient had not eaten well prior to the test.

The steadily mounting experimental evidence that thiamin plays a rôle in the intermediary metabolism of carbohydrates (18) has aroused considerable interest in the status of diabetics with regard to this vitamin (19). Of particular interest is the relationship of "diabetic neuritis" to the peripheral neuritis of beriberi. All of 6 regulated diabetics studied showed excretory values in the normal range. These patients had all been on diets of adequate thiamin content before coming

TABLE V

Urinary excretion of thiamin by patients with gastro-intestinal disease

Case number	Sex	Age	Diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Antacid medication during test	Thiamin excreted in urine		Fraction of oral dose in urine	Comment
							Before oral dose	After oral dose		
		years					*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*	
46	M	39	Marginal ulcer	Adequate	Good	$CaCO_3$ 1 gram and $Mg_2Si_3O_8$ 0.5 grams q. 1 hour	99	792	13.9	2 years after gastro-enterostomy
47	M	25	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	34	720	13.7	Recent chronic hemorrhage
48	M	34	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	15	630	12.3	Recent chronic hemorrhage
49	M	58	Atrophic gastritis	Adequate	Good	Colloidal $Al(OH)_3$ 6 cc. q. 1 hour	41	625	11.7	8 days after large hematemesis
50	M	29	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	32			
51	M	56	Gastric ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	31			X-ray showed ulcer healed at time of test
52	M	66	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	63	594	10.6	Mild chronic pyloric obstruction
53	M	65	Duodenal ulcer	Adequate	Good	Colloidal $Al(OH)_3$ 6 cc. q. 1 hour	30	492	9.2	Recent chronic hemorrhage
54	M	58	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams q. 2 hours	46			
55	M	49	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 mgm. q. 1 hour	21	428	8.1	Just after relief of partial obstruction
56	M	56	Recurrent marginal ulcer	Adequate	Good	Colloidal $Al(OH)_3$ 4 cc. q. 1 hour	43	373	6.6	19 years after gastro-enterostomy
57	M	56	Duodenal ulcer	Suboptimal	Good	Colloidal $Al(OH)_3$ 8 cc. q. 1 hour	38	366	6.6	Recurrent hemorrhages for 10 years
58	M	47	Duodenal ulcer	Adequate	Good	Colloidal $Al(OH)_3$ 6 cc. q. 1 hour	33	258	4.5	Tests on 4th and 5th hospital day
59	M	46	Duodenal ulcer	Suboptimal	Good	Colloidal $Al(OH)_3$ 6 cc. q. 2 hours	26	123	1.9	4 days after recovery from alkalosis

TABLE V—*Continued*

Case number	Sex	Age	Diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Antacid medication during test	Thiamin excreted in urine		Fraction of oral dose in urine	Comment
							Before oral dose	After oral dose		
		years					*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*	
60	F	38	Gastric carcinoma	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	32	590	11.2	Severe hemorrhage 5 weeks before
61	F	57	Duodenal ulcer	Adequate	Good	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	21	368	6.9	
62	F	29	Duodenal ulcer	Suboptimal	Good	Colloidal $Al(OH)_3$ 8 cc. q. 1 hour	24	215	3.8	
63	F	26	Gastric ulcer	Adequate	Good	$Mg_2Si_3O_8$ 1 gram q. 1 hour	46	726	13.6	30 cc. liquor hepatis daily for 1 week before test
64	M	38	Tuberculous peritonitis	Adequate	Good (700 γ)	$CaCO_3$ 2 grams or $MgCO_3$ 2 grams q. 1 hour	34	390	7.1	Biopsy diagnosis
			10 weeks later	Excellent	High (1250 γ)	None	238	1800	31.2	Clinically quiescent for 6 weeks
65	M	49	*Total* gastrectomy	Adequate for 7½ weeks	Good (800 γ)	None	68	456	7.8	Carcinoma of stomach: resection 10 weeks before test
66	M	54	Pernicious anemia	Suboptimal	Fair	None	44	684	12.8	Mild posterolateral sclerosis
67	M	73	Pernicious anemia	Inadequate	Fair (600 γ)	None	12	324	6.2	Mild posterolateral sclerosis
68	M	53	Pernicious anemia	Inadequate	Fair (500 γ)	None	12	60	1.0	No neurological abnormality
69	M	55	Abdominal carcinomatosis	Inadequate	Low (300 γ)	None	50			Primary in stomach
70	M	47	Subacute toxic hepatitis	Suboptimal	Fair	None	59	216	3.1	Severe jaundice. Biopsy diagnosis
71	F	44	Advanced atrophic cirrhosis	Suboptimal	Fair (500 γ)	None	38	207	3.4	
72	M	53	Atrophic cirrhosis. Chronic alcoholism	Suboptimal	Fair (500 γ)	None	47			

to the hospital and none of them showed evidence of ketosis, although 2 showed intermittent glycosuria and hyperglycemia. Balance studies with more careful attention to the state of control of the diabetes are expected to give more conclusive information.

Patients with gastro-intestinal disease. Nineteen cases were studied while being treated by a modified Sippy regimen for peptic ulcer; subsequently 3 of these were shown to have atrophic gastritis, tuberculous peritonitis, and gastric carcinoma respectively, rather than ulcer. These tests, with one exception, were done after the patients had been under treatment for 2 or more weeks. Most of the patients had been on good diets before hospitalization. Preceding and during the tests they ate their diets well. Calculations of these diets showed a daily intake of 700 to 900 micrograms of thiamin with a thiamin-non-fat-calorie ratio of approximately 1.0. Antacid medication was continued during the test period.

The results are presented in Table V. The values before the oral dose are definitely lower than those obtained from normal subjects except for 1 case; however, only 5 of the 16 given oral test doses excreted less than 7 per cent thereof. This type of response, a low value during the period when the sole source of thiamin is the diet

followed by excretion of a normal fraction of the oral dose, was observed in normally nourished subjects after subsisting for a few days on an experimentally deficient diet (2). Since the patients on the modified Sippy regimen are known to have ingested an adequate diet during the test, it is suggested that the antacid medication may be the factor responsible for the low urinary thiamin values. This may be due either to destruction of the dietary thiamin in the gastro-intestinal tract when alkali is given simultaneously, or to loss of the vitamin by way of the feces due to adsorption of the alumina gels or silicates. The results in Case 63 support this concept: despite the fact that this patient had received whole vitamin B complex supplements for 1 week prior to the test, the excretion before the oral dose was only 46 micrograms, followed by a percentage excretion of the oral dose well in the normal range. Studies reported previously (1) have ruled out the possibility that these results are due to destruction of thiamin by alkaline urine in the bladder.

A somewhat comparable situation might be anticipated in patients with achlorhydria. Case 65 was studied 10 weeks after a total gastric resection for carcinoma; he had ingested and retained a diet of adequate thiamin content for over 7 weeks prior to the test. He excreted less dietary thiamin than did the normal subjects, but the fraction of the oral dose excreted was not definitely low. One of 3 patients with pernicious anemia had values very similar to those patients receiving antacid medication, while the other 2 showed low values both before and after the oral dose.

The low excretory values obtained on the 3 cases of hepatic disease studied are of interest in view of the widely held opinion that the liver has an important rôle in the handling of thiamin (18). However, the results in these cases may be attributed to the preceding suboptimal thiamin in-

TABLE VI

Urinary excretion of thiamin by patients with various other diseases

Case number	Sex	Age	Clinical diagnosis	Thiamin content of previous diet	Dietary thiamin during test	Thiamin excreted in urine		Fraction of dose excreted in urine	Comment
						Before oral dose	After oral dose		
		years				*micrograms per 24 hours*	*micrograms per 24 hours*	*per cent*	
73	M	45	Brucellosis	Inadequate	Good (700 γ)	47	176	2.6	Mild peripheral neuritis
74	M	62	Carcinoma and osteomyelitis of mandible	Inadequate	Fair	38			
75	M	55	Chronic alcoholism	Adequate	Good	96			
76	M	48	Myalgia	Suboptimal	Fair (550 γ)	43	460	8.3	
77	M	46	Impotence	Adequate	Good	218	855	12.7	
78	M	52	Progressive peripheral polyneuritis	Adequate	Good	208	1386	23.6	Unaffected by thiamin therapy
79	M	55	Chronic glomerulotubular nephritis with uremia	Adequate	Good (700 γ)	23	165	2.8	N.P.N. 100 to 75 mgm. per cent
80	F	36	Chronic glomerulotubular nephritis	Suboptimal	Fair (570 γ)	43	445	8.0	N.P.N. normal
81	F	23	Neurocirculatory asthenia	Suboptimal	Fair	26	384	7.2	
82	F	19	Hysteria	Suboptimal	Good (700 γ)	46	435	7.8	
83	F	42	Sciatic neuralgia	Adequate	Good	53	536	9.7	
84	F	55	Bronchopneumonia	Adequate	Good	115	1002	17.7	Tested during convalescence
85	F	20	Gastro-intestinal allergy	Adequate	Fair	85			
86	F	45	Periarthritis shoulder	Adequate	Good	154			
87	F	40	Migraine	Adequate	Good	172			
88	F	28	? retrobulbar neuritis	Adequate	Good	130	1090	19.2	
89	F	23	Anxiety state	Adequate	Good	200			

take as well as to an impairment of storage in the body.

Patients with miscellaneous diseases. The results obtained on 17 patients with various other diseases are presented in Table VI. The low values for thiamin excretion by Case 73 suggest that the mild peripheral neuritis which complicated his brucellosis might well be attributed to a thiamin deficiency; however, it was impossible to carry out therapy suitably controlled to rule out a toxic etiology. Case 79 with terminal nephritis and chronic nitrogen retention had eaten an adequate diet for 4 weeks before the test; the low urine values obtained may indicate that in renal insufficiency the kidney is unable to excrete thiamin. Among the other cases in this group there is apparent some correlation between the thiamin content of the preceding diet and the values for urinary thiamin excretion.

DISCUSSION

The correlation in the individual subject between the urinary excretion of thiamin before and after the oral test dose is concordant when judged by the above standards in 68 of the 75 cases in which both values were obtained, excluding patients with achlorhydria and those receiving antacid medication. We have observed only 1 subject (Case 30, Table III) in whom a normal value for the 24-hour excretion was followed by excretion of an abnormally small fraction of the test dose. The remaining 6 subjects excreted a normal fraction of the test dose despite a preceding 24-hour value in the definitely low range; 4 of these were known to have eaten poorly on the day of the test. These results are interpreted as indicating that insufficient thiamin from dietary sources was available for absorption from the gastro-intestinal tract on the day of the test, but that there was no significant depletion of the thiamin stores. Experimental evidence for this interpretation is presented elsewhere (2).

The results in the patients with achlorhydria and those receiving antacid medication suggest that in these cases diagnostic significance should be attached only to the fraction of the test dose excreted. They also indicate that factors in the gastro-intestinal tract which affect the availability of thiamin for absorption may be of clinical significance. Preliminary studies indicate that a significant reduction in urinary thiamin excretion follows the administration of antacid medications to patients on a constant dietary intake. Results of preliminary studies on the stability of thiamin *in vitro* in the secretions of the gastro-intestinal tract indicate that the vitamin is stable in achlorhydric and in normal gastric juice from its natural acidity to pH of 8. However, significant losses occur in pancreatic juice and bile at the natural pH of 8, but not at pH 4.5. It is suggested that with gastric acidity neutralized or absent the contents of the small intestine may become alkaline enough to permit an abnormal destruction of thiamin.

In discussing standards of normality and deficiency, it is important to bear in mind that low values for urinary thiamin can in themselves indicate no more than a depletion of the body stores of this particular food factor. From the data presented in the tables it is obvious that there is no particular level of urinary thiamin excretion at which signs and symptoms of thiamin deficiency appear. The *clinical* significance of the finding of thiamin subnutrition in a patient who presents none of the recognized clinical features of thiamin deficiency is uncertain. Before the physiologic alterations and clinical symptoms associated with the wide variety of diseases presented in this paper can be attributed to thiamin deficiency, it will be necessary to evaluate the response of such cases to thiamin therapy under carefully controlled conditions, or to demonstrate a specific biochemical dysfunction.

SUMMARY AND CONCLUSIONS

Under proper conditions, the level of the urinary excretion of thiamin permits an objective determination of the state of thiamin nutrition in the human subject.

There is good correlation between the urinary thiamin values and the adequacy of the preceding diet with respect to this vitamin. The 24-hour urinary thiamin excretion in subjects whose previous dietary intake of thiamin had been adequate, and who ingested an adequate diet on the day of the test, was 90 micrograms or more in all males, and above 60 micrograms in all females but one. Under similar conditions, the 24-hour excretion in

subjects whose previous diet had been definitely inadequate in thiamin was 66 micrograms or below in all males, and 43 micrograms or below in all females except one. All subjects with a preceding adequate thiamin intake excreted over 7.5 per cent of an oral test dose of 5 mgm. of thiamin given with the largest meal of the day. All subjects whose previous diets had been definitely inadequate excreted less than 7 per cent of such a test dose.

Three patients with "alcoholic beriberi" excreted abnormally small amounts of thiamin in the urine.

About half the patients presenting clinical evidence of deficiencies in other food factors had urinary values indicative of thiamin subnutrition.

Six of the 7 patients with cardiac decompensation due to organic heart disease had values indicative of thiamin subnutrition.

Six patients with regulated diabetes mellitus had urinary thiamin excretions in the normal range.

Six of 7 patients with hyperthyroidism had urinary thiamin values in the normal range. The 1 patient in this group with definitely low values had been on an inadequate thiamin intake for a relatively short time.

Patients receiving antacid medication for peptic ulcer and patients with achlorhydria excreted abnormally small amounts of thiamin in the urine when the diet furnished the entire source of the vitamin. However, most of these patients excreted a normal fraction of the oral test dose.

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