By putting (1) into (2), we obtain

$$T=[\frac{1}{V_p}+\frac{h}{a}\cdot(T_{cp}-\frac{a+1}{V_p})/(A\cdot d\cdot S) \quad (3)$$

This equation indicates the linear dependence of passage time on hematocrit. Since V_p can be determined from the measurement at $H=0$, T_{cp} for the blood from the normal subjects is estimated to be 0.85 ± 0.10 msec (mean $\pm$ SD). If we can assume that V_p for plasma of patients' blood is the same as the normal value (according to Dintenfass[5], plasma viscosity in renal failure does not differ from the normal value), T_{cp} for the patients' blood is estimated to range from 1.16 to 3.14 msec. In other words the increment of the passage time of the patients' blood can be attributed to a reduction of the red cell deformability in an agreement with Dintenfass[5] who deduced a reduced deformability of red cells from blood viscosity measurements in renal failure. The relation of the deformability with BUN-value is unclear, but as seen in figure 2, hemodialysis seems to ameliorate the deformability of red cells of the patients. The reduced red cell deformability will increase red cell trapping at the spleen, which may be one of the causes of the anemia in renal failure.

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An experimental study of thiamine metabolism in acute ethanol intoxication[1]

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Summary. A dose of 3.9 g/kg b.wt of ethanol was administered to rabbits, and ethanol and thiamine concentrations, transketolase activity and thiamine pyrophosphate (TPP) effect in blood samples were determined. It was established that ethanol ingestion produced a rapid decrease in blood thiamine levels and transketolase activity in erythrocytes and an increase in TPP effect in erythrocytes. These values reverted to normal within 2 or 3 days after the ingestion of alcohol.

Alcoholics are nearly always in a state of thiamine deficiency[2–4], and although this deficiency may be partially attributed to a low dietary intake of thiamine[5] other mechanisms are also probably involved[6,7]. A number of experimental studies on the relationship between thiamine metabolism and chronic ethanol administration have been done, but since there is little information on thiamine metabolism in cases of acute ethanol intoxication, we carried out studies in an attempt to clarify the relation.

Materials and methods. Male rabbits, *Oryctolagus cuniculus* var. *domesticus,* weighing about 2500–3000 g were used. A restricted diet (100 g/day) of commercial rabbit chow (Oriental Co., Japan, thiamine concentration: 0.8 mg/100 g) was ingested by every rabbit during the experimental period. A dose of 13 ml/kg b.wt of 30% ethanol (about $\frac{1}{3}$ of LD_{50}) was administered orally by a gastric tube, and blood samples were obtained from the vena praeauriculares. In the control rabbits, 14.2 ml/kg of 50% glucose was administered by a gastric tube to equalize the energy intake.

Ethanol concentration was determined by the method of Eriksson[8] with several modifications. A 0.2 ml aliquot of blood was placed in a 10 ml vial to which 0.2 ml of n-propanol solution (1 g/l n-propanol in isotonic saline) was added. The vial was sealed with a butyl rubber septum, then heated at 55 °C for 20 min. A 1.0 ml volume of the head-space gas was injected into a gas chromatograph, and chromatography was performed with an instrument equipped with a flame ionization detector (Shimadzu Co., Japan, model GC-4BMPFE). A glass column (2m) packed with 15% polyethylene glycol 1500 on chromosorb (60–80 mesh) was used. Detector temperature was maintained at 150 °C, the injection temperature at 150 °C, the oven temperature at 80 °C and the nitrogen flow rate at 70 ml/min. Glucose was determined by the method of Hultman[9]. Thiamine was determined by the thiochrome method of Fujiwara and Matsui[10]. Transketolase (EC 2.7.1.1) activity was assayed by the method described by Itokawa[11]. The thiamine pyrophosphate (TPP) effect is the percentage stimulation of enzyme activity above the origi-

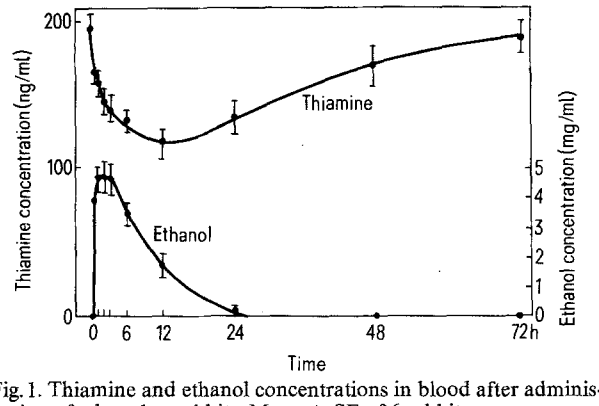

Fig. 1. Thiamine and ethanol concentrations in blood after administration of ethanol to rabbits. Mean ± SE of 6 rabbits.

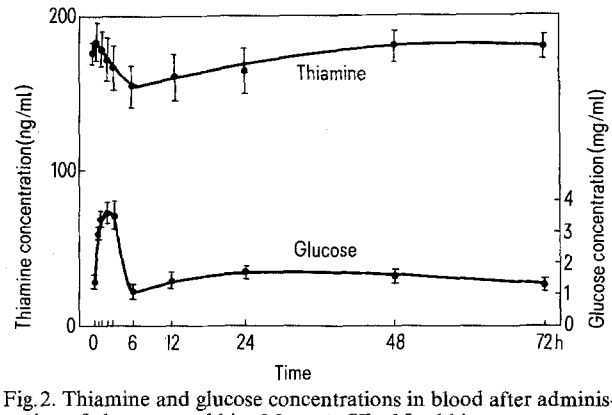

Fig. 2. Thiamine and glucose concentrations in blood after administration of glucose to rabbits. Mean ± SE of 5 rabbits.

nal transketolase activity produced by adding TPP to the sample before assay. Therefore, the TPP effect reflected the proportion of the apoenzyme which was not saturated with thiamine[12].

Results. After a few minutes of ethanol ingestion, the rabbits seemed to be quite intoxicated and remained prostrate for about 4–5 h. Nystagmus was observed from 15 min to 3 h after ethanol ingestion. Figure 1 shows the time course of ethanol and thiamine concentrations in blood after ethanol ingestion. Ethanol in the blood increased rapidly and reached a peak in 1–3 h, then decreased. Thiamine concentration in the blood decreased gradually and after 12 hours thiamine levels reached the lowest value, then increased slowly and reverted to normal after 72 hours.

Figure 2 shows the glucose and thiamine concentrations in the blood after the administration of glucose. Blood glucose increased sharply 1-3 h after glucose ingestion, and then decreased rapidly. Thiamine levels in blood decreased slightly 6 h after glucose ingestion; however, the decrease was not statistically significant.

Table 1 shows the transketolase activity and TPP effect in erythrocytes of rabbits given ethanol or glucose. After ethanol ingestion, transketolase activity decreased and the TPP effect increased. These values reverted to normal after 48–72 hours. In contrast, decrease in transketolase activity and TPP effect after glucose ingestion was slight and transient.

Table 1. Transketolase activity and TPP effect in erythrocytes after administration of ethanol or glucose

Time after administration (h)	Transketolase activity (mg sedoheptulose produced/ml/h)		TPP effect (%)	
	Administration of Ethanol	Glucose	Administration of Ethanol	Glucose
0	1.75±0.09	1.66±0.19	3.69±2.42	2.48±2.02
0.5	1.54±0.12	1.54±0.26	8.38±5.20	3.78±2.63
1	1.48±0.11	1.26±0.17*	15.20±9.84	26.80±9.77*
2	1.34±0.13*	1.36±0.19	17.50±4.33*	20.86±10.36
3	1.26±0.09*	1.36±0.27	22.93±4.14*	12.33±3.75
6	1.23±0.15*	1.62±0.30	30.08±7.35*	8.52±3.65
12	1.34±0.15*	1.64±0.18	21.13±4.65*	2.55±1.84
24	1.48±0.20	1.63±0.25	14.08±4.89	2.18±1.55
48	1.67±0.09	1.66±0.26	11.23±3.34	3.43±1.52
72	1.67±0.09	1.69±0.28	8.78±4.40	1.18±0.91

Values represent mean ± SE of 6 rabbits (ethanol group) and 5 rabbits (glucose group). * Significant difference ($p<0.05$) as compared with the value of 0 h analyzed by the Student t-test.

Table 2. Free and total thiamine levels in whole blood and thiamine levels in plasma after ethanol ingestion

		Before ethanol ingestion	12 h after ethanol ingestion
		(ng/ml)	(ng/ml)
A	Free thiamine in blood	38.9±8.8	13.2±3.2***
B	Total thiamine in blood	168.4±9.2	116.7±8.6**
B-A	Phosphorylated thiamine in blood	128.8±6.9	103.6±7.2*
		(%)	(%)
A/B		23.5±1.3	10.9±2.5**
		(ng/ml)	(ng/ml)
C	Total thiamine in plasma	108.8±8.3	51.5±3.2***
D	Total thiamine in blood cells	245.6±17.8	179.5±14.7*
		(%)	(%)
C/D		44.6±2.6	28.8±1.6***

Values represent mean ± SE of 6 experiments. Significant difference * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$) as compared with the values before ethanol ingestion.

Table 2 shows the concentrations of free and phosphorylated thiamine in blood and total thiamine in plasma and blood cells before, and 12 hours after, ethanol ingestion. Free thiamine decreased markedly in contrast to phosphorylated thiamine. The decrease of thiamine was more significant in the plasma than in blood cells.

Discussion. Our results showed that ingestion of ethanol produced a temporary fall in thiamine levels and transketolase activity in the blood. As 3 days were required for a reversion to normal levels, it is probable that long term ingestion of ethanol would induce a severe thiamine deficiency.

Thiamine is required as a cofactor in intermediary carbohydrate metabolism; however, it is worthy of note that the decrease in blood thiamine after ethanol ingestion was much greater than after the isocaloric glucose administration.

This observation coupled with the findings that ratios of free thiamine to total thiamine and plasma thiamine to whole blood thiamine were decreased significantly after ethanol ingestion, lead to the assumption that there is a metabolic pathway for ethanol in some tissues which requires thiamine as a cofactor, as free thiamine and plasma thiamine are considered to be easily-available thiamine for other tissues.

Thiamine on the one hand plays an important role in intermediary carbohydrate metabolism and, on the other hand, a significant role in nerve excitation which is independent of the coenzyme role of thiamine[13–17]. The nystagmus seen in the ethanol administered rabbits could be related to the impairment of the second role of thiamine.

In the time course study, hematocrit values were determined in each blood sample after ethanol and glucose administration, and with the frequent blood letting, a decrease was observed to the same extent in both groups. The minimum hematocrit value (70% of the normal value) was detected 72 h after ethanol and glucose administration, however, the effects of hematocrit on thiamine levels in whole blood were calculated to be negligible.

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