after resuscitation is as important as the management of the arrest; cardiac arrest is but one aspect of the patient's illness. The problem of after-care is reflected in the 25 patients in Group 2 in whom the circulation was restored but who subsequently died. Recurrent cardiac arrest, however, is no bar to long-term survival; 3 long-term survivors had a total of 7 cardiac arrests. One man had 3 cardiac arrests in forty-eight hours until the commencement of catheter pacing; he is alive and well over one year later.

Acid-base Data

Arterial blood was taken in 38 patients after the administration of 200 mEq of sodium bicarbonate, to assess the adequacy of this treatment. It was not possible accurately to determine the time from cardiac arrest to arterial sampling. Analysis for pH, carbon dioxide tension and oxygen saturation was carried out immediately.

pH: In general the long-term survivors had a pH nearer the normal range than the remainder. In 22 patients pH was less than 7·3, indicating an acidosis; in 6 pH was below 7·0, indicating a severe acidosis.

Bicarbonate: Plasma bicarbonate was less than 20 mEq/l in 16, indicating a metabolic acidosis, but it was severe in only 6, which suggests that 200 mEq of sodium bicarbonate had been effective.

Carbon dioxide tension: Despite attention to ventilation, alveolar underventilation (carbon dioxide tension over 45 mmHg) occurred in 23 of the 38 patients, and in 9 this was severe. In the remainder more vigorous ventilation resulted in a fall in carbon dioxide tension.

Correction of acidosis: Adequate ventilation is vitally important not only to prevent respiratory acidosis but also for the correction of metabolic acidosis by the administration of sodium bicarbonate. During the period of circulatory arrest before the commencement of massage and during the period of low cardiac output produced by massage there is marked tissue hypoxia which results in the release of lactic acid from anaerobic metabolism. Sodium bicarbonate relieves the acidosis by combining with lactic acid to form carbonic acid which dissociates into carbon dioxide and water. This reaction can only proceed to completion if carbon dioxide is eliminated from the lung.

Oxygen: Oxygen saturation often appears satisfactory but when the alveolar-arterial oxygen tension gradients are calculated a different pattern emerges. This gradient was increased several fold in every patient indicating a gross disturbance of gas transfer. This may be the result of (1) a disturbance of ventilation/blood flow relationship in the lung, (2) venous admixture, or (3) impairment of diffusion. The combination of a low cardiac output and positive pressure ventilation will inevitably disturb ventilation/blood flow relations but the other mechanisms may also be contributory.

Conclusions

Acidosis by decreasing myocardial contractility, perpetuating arrhythmias and antagonizing vasopressors is harmful. The metabolic component can be corrected by giving 200 mEq of sodium bicarbonate and the respiratory component by adequate ventilation. Hypoxæmia occurs frequently, therefore 100% oxygen should be administered as early in resuscitation as possible. Attention to these details will increase the number resuscitated.

Studies on Blood Keto Acids in Vitamin Deficiency

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Several vitamins function as cofactors for enzyme systems, and in vitamin deficiency the activity of these enzymes may be impaired so that intermediary metabolites accumulate. Of interest in vitamin deficiency may be the occurrence of an interference with intermediary carbohydrate metabolism and mechanisms for energy production.

A major pathway by which carbohydrate is utilized is the glycolytic route, during which pyruvic acid is formed which is later broken down to acetyl coenzyme A. The latter, in addition, is also derived from the breakdown of fat, and therefore forms a common meeting point in the oxidation of both fat and carbohydrate. Acetyl coenzyme A condenses with oxaloacetate and enters the Krebs cycle for final breakdown. Impairment of glycolysis may be reflected in an alteration in the concentration of pyruvic acid in the blood and tissues, whereas impairment of the Krebs cycle may be reflected in alterations in the concentration of α-oxoglutaric acid and other components of the cycle.

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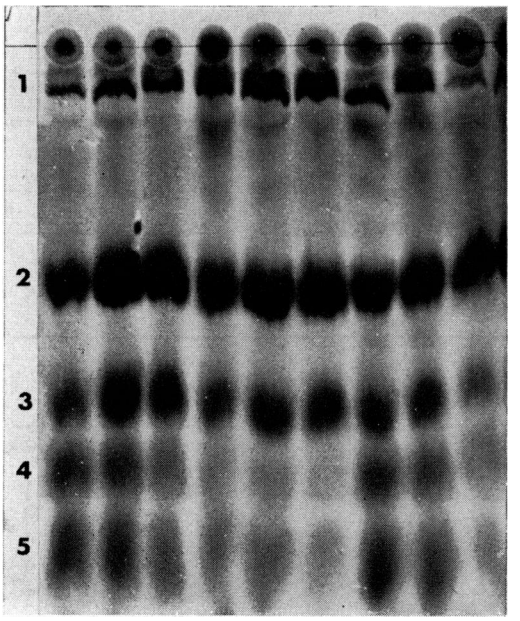

Fig 1 *Blood keto acids. Chromatogram of keto acid 2 : 4-dinitrophenylhydrazones.* 1, *α-oxoglutaric acid.* 2, *pyruvic acid, slow component.* 3, *pyruvic acid, fast component.* 4, *α-oxoisocaproic acid, slow component, and α-oxoisovaleric acid.* 5, *α-oxoisocaproic acid, fast component, and α-oxo β-methyl valeric acid*

The concentrations of blood pyruvic and α-oxoglutaric acids have been determined in certain vitamin deficiency states. Previous studies on pyruvic acid using standard colorimetric methods, such as that of Friedemann & Haugen (1943), have the disadvantage in that they are not specific and measure in addition other α-keto acids, indeed pyruvic acid may account for only 50-70% of the total measured (Cavallini *et al.* 1949, El Hawary & Thompson 1953). On the other hand, chromatography of their 2:4-dinitrophenylhydrazone derivatives allows of their individual separation and measurement (Cavallini *et al.* 1949, El Hawary & Thompson 1953, McArdle 1957). Blood pyruvic and α-oxoglutaric acids were therefore estimated chromatographically (Fig 1) as described elsewhere (Buckle 1963, 1966). They were estimated following a fourteen-hour fast and again one and one-and-a-half hours after 100g oral glucose (Joiner *et al.* 1950). The mean values of pyruvic and α-oxoglutaric acids in normal subjects are shown in Table 1.

Vitamin B_1 (Thiamine) Deficiency

Chronic alcholics and malnourished individuals: Table 1 also shows the mean levels of blood pyruvic and α-oxoglutaric acids (together with their standard errors) in a series of chronic alcoholics and malnourished individuals; in some there was an associated peripheral neuropathy, but in none was there any evidence of cardiac failure or cirrhosis. A marked elevation of pyruvic and α-oxoglutaric acids was demonstrated in the patients with peripheral neuropathy. Elevation of pyruvate and α-oxoglutarate was also demonstrated in the patients assessed as being deficient of thiamine on the basis of their dietary intake, but not showing any clinical manifestations associated with the deficiency; although the corresponding values were not so high as in the patients with peripheral neuropathy. In the group of vagrants and alcoholics judged not to be deficient the levels of both keto acids were normal.

Treatment with thiamine (30 mg daily intramuscularly for five to ten days led to a fall to normal in the elevated levels of both pyruvate and α-oxoglutarate (Fig 2).

Wernicke's encephalopathy: Evidence suggests that Wernicke's encephalopathy may be associated with a deficiency of thiamine (de Wardener & Lennox 1947, Cruickshank 1950, Phillips *et al.* 1952). Table 2 shows the mean values of pyruvic and α-oxoglutaric acids (with their standard errors) in a group of 4 patients with Wernicke's encephalopathy. A marked elevation of both keto

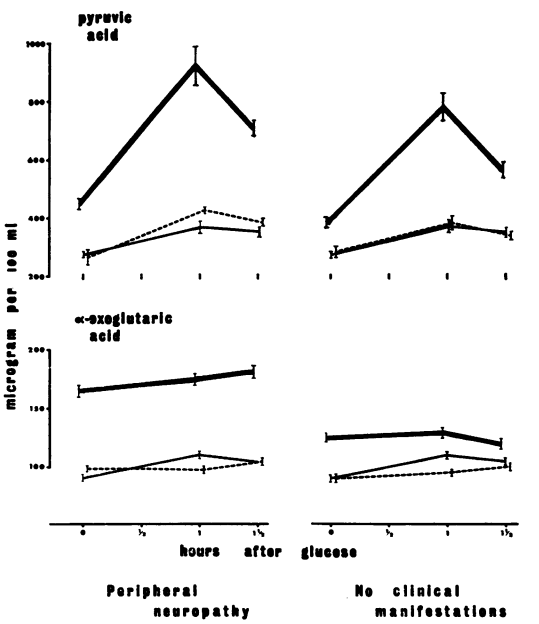

Fig 2 *Blood keto acids in patients with vitamin B_1 (thiamine) deficiency. Effect of treatment with thiamine. Mean values are shown, together with the standard error of the mean.* ——— *initial values.* ------ *values following treatment with thiamine.* ——— *control normal values*

Table 1

Concentrations of blood pyruvic and α-oxoglutaric acids in normal subjects and in chronic alcoholics and malnourished individuals

	Concentration of blood keto acids (mean values in μg/100 ml)					
	Pyruvic acid			*α-oxoglutaric acid*		
	Fasting	*1 hour after glucose*	*1½ hour after glucose*	*Fasting*	*1 hour after glucose*	*1½ hour after glucose*
Normal controls (35 subjects)	275± 7·8	372± 13·8	352±16·1	91± 7·6	111±10·1	105± 9·7
Thiamine deficiency:						
Patients with peripheral neuropathy (8 patients)	449±17·7	927±130·5	708±44·7	164±19·8	175±21·8	181±23·2
Patients without any clinical manifestations (9 patients)	384±34·4	786± 92·3	528±45·7	128±12·4	129±17·0	118±17·8
Vagrants and alcoholics without evidence of thiamine deficiency (9 patients)	254±15·9	357± 16·3	339±36·7	97±16·1	100±13·8	103±20·2

Table 2

Concentrations of blood pyruvic and α-oxoglutaric acids in Wernicke's encephalopathy

	Concentration of blood keto acids (mean values in μg/100 ml)					
	Pyruvic acid			*α-oxoglutaric acid*		
	Fasting	*1 hour after glucose*	*1½ hour after glucose*	*Fasting*	*1 hour after glucose*	*1½ hour after glucose*
Patients with Wernicke's encephalopathy (4 patients):						
Initial values	494±55·1	940±20·5	661±75·1	259±25·1	263±26·6	249±23·6
Values following treatment with thiamine	289±12·2	376±13·9	352±15·9	96± 4·4	113± 4·4	107± 4·3

Table 3

Concentrations of blood pyruvic and α-oxoglutaric acids in cardiac failure

	Concentration of blood keto acids (mean values in μg/100 ml)					
	Pyruvic acid			*α-oxoglutaric acid*		
	Fasting	*1 hour after glucose*	*1½ hour after glucose*	*Fasting*	*1 hour after glucose*	*1½ hour after glucose*
Heart failure, presumptive thiamine-deficient (5 patients):						
Initial values	777±37·9	1,789±13·0	1,245± 9·1	331±25·8	333±21·9	343±19·2
After treatment with thiamine	262±16·6	361±10·7	325±16·9	102± 2·7	106± 4·1	108± 4·1
Cardiomyopathy (7 patients)	285±18·9	396±22·8	369±26·2	103± 3·0	106± 5·1	103± 3·6
Heart failure (ischæmic and valvular) (7 patients)	289±15·7	396±18·5	373±24·3	103± 3·4	108± 3·3	106± 2·8

Table 4

Concentrations of blood pyruvic and α-oxoglutaric acids in vitamin B_{12} deficiency (reproduced from Buckle, 1966, by kind permission)

	Concentration of blood keto acids (mean values in μg/100 ml)					
	Pyruvic acid			*α-oxoglutaric acid*		
	Fasting	*1 hour after glucose*	*1½ hour after glucose*	*Fasting*	*1 hour after glucose*	*1½ hour after glucose*
All cases (33)	384±14·7	659±30·1	569±21·1	64±2·5	66±3·9	68±2·9
Patients with uncomplicated vitamin B_{12} deficiency (17 patients)	389±26·6	661±46·0	575±33·0	64±3·6	67±3·6	69±4·4
Patients with neurological manifestations of vitamin B_{12} deficiency (16 patients)	377± 6·5	657±38·6	562±26·1	63±3·5	65±4·7	68±4·5

acids was demonstrated and the levels of both fell to normal following treatment with thiamine (30 mg daily intramuscularly for five days).

Heart failure in alcoholics: The occurrence of thiamine deficiency in oriental beriberi is well recognized, but in this country the role of thiamine deficiency in causing heart failure is less well established. Thiamine deficiency occurs most commonly in association with alcoholism, but alcohol itself may have a direct toxic action on the myocardium, and this effect, rather than any deficiency of thiamine, may be a factor involved in the development of alcoholic cardiomyopathy (Brigden 1957). Table 3 shows the mean values of pyruvate and α-oxoglutarate (with their standard errors) in a group of 5 patients aged 28-49 who had been drinking heavily and living on an

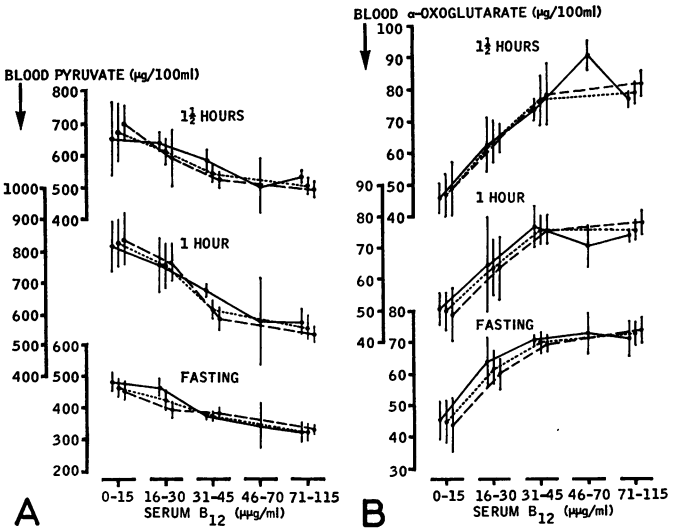

Fig 3 *Blood keto acids in relation to the serum vitamin B_{12} concentration.* A, *pyruvic acid.* B, *α-oxoglutaric acid. Fasting, 1 hour, and 1½ hour post-glucose values are shown. Mean values are given together with their standard deviations.* ●——●, *mean values for patients with uncomplicated vitamin B_{12} deficiency.* ● - - - - ●, *mean values for patients with neurological manifestations.* ● - - - - ●, *mean values for all patients with vitamin B_{12} deficiency. Number of patients for each serum vitamin B_{12} concentration (μμg/ml) are:*

	0–15	*16–30*	*31–45*	*46–70*	*71–115*
Patients with uncomplicated vitamin B_{12} deficiency	4	3	2	3	4
Patients with neurological manifestations	3	4	4	–	4

(*Reproduced from Buckle, 1966, by kind permission*)

inadequate diet, and who presented with acute symptoms of heart failure. The levels of both keto acids were abnormally elevated and fell to normal following thiamine (30 mg daily). In 7 cases of cardiomyopathy, 3 of whom were idiopathic whilst in 4 there was a history of regular drinking, the mean concentrations of both keto acids were normal. Similarly, in a group of 7 patients with heart failure due to ischæmia or valvular disease the levels of both keto acids were normal.

Vitamin B_{12} Deficiency

Impaired carbohydrate metabolism has been demonstrated in experimental vitamin B_{12} deficiency (Ling & Chow 1952, 1954), whilst in subacute combined degeneration of the cord elevated blood pyruvate has been found (Earl *et al.* 1953, Hornabrook & Marks 1960). Blood pyruvic and α-oxoglutaric acids have been measured in 33 patients with vitamin B_{12} deficiency, and the abnormal elevation of pyruvate has been confirmed, but the level of α-oxoglutaric acid has been found to be abnormally low (Buckle 1966). Table 4 shows the mean values of the keto acids (with their standard errors) in 17 patients with uncomplicated vitamin B_{12} deficiency as compared with the values for the 16 patients in whom there was evidence of neurological involvement, namely peripheral neuropathy or subacute combined degeneration. No significant difference could be detected for the corresponding values of either keto acid between the 2 groups. In a similar manner the degree of abnormality of either keto acid was independent of the severity of the anæmia. However, the degree of keto acid abnormality became more marked the greater deficiency of vitamin B_{12} (Fig 3). As the concentration of serum B_{12} fell so the degree of elevation of pyruvate and depression of α-oxoglutarate increased in extent.

Treatment with vitamin B_{12} led to a return to normal of the previously elevated pyruvate and depressed α-oxoglutarate (Fig 4). The improve-

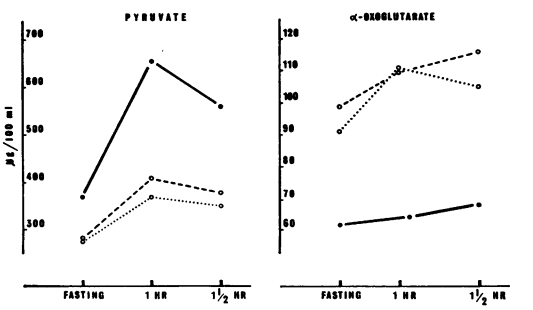

Fig 4 *Blood keto acids in vitamin B_{12} deficiency. Effects of treatment with vitamin B_{12}. Mean fasting, 1 hour, and 1½ hour post-glucose values are shown for all 33 patients.* ●——●, *mean values initially before treatment.* ○ - - - - ○, *mean values following treatment with vitamin B_{12}.* ○ · · · · ○, *mean values in normal control subjects*

ment first occurred after two to three days' treatment and maximal improvement was achieved in five to seven days.

Folic Acid Deficiency

Studies in a few patients with folic acid deficiency suggest that abnormal keto acid metabolism may occur and is reversed by specific treatment with folic acid. However, sufficient data to permit firm conclusions are not yet available.

Comment

The abnormality of pyruvic acid metabolism in thiamine deficiency may be explained, at least in part, by the role that thiamine plays in being an essential cofactor for the pyruvate oxidase system (Peters 1936). In thiamine deficiency impairment of pyruvate oxidase activity will lead to an interference in the rate of breakdown of pyruvate which will therefore accumulate. But thiamine also functions as part of an essential coenzyme for the decarboxylation of other α-oxoacids (Sebrell & Harris 1954). Consequently, the rise in blood α-oxoglutaric acid demonstrated may have been due to an impairment in its rate of decarboxylation in a manner comparable with that responsible for the rise in pyruvate.

In vitamin B_{12} deficiency the accumulation of pyruvic acid may also be due to impairment of pyruvate oxidase activity; for the activity of pyruvate oxidase is dependent on the concentration in its reduced form of its component sulphydryl groups (Peters & Wakelin 1946). Decreased concentrations of soluble sulphydryl compounds have been demonstrated in vitamin B_{12} deficiency (Dubnoff 1950, Register 1954). The effect of vitamin B_{12} deficiency may therefore be due to a lack of total reductive capacity of the cobamide coenzyme in keeping the sulphydryl groups of pyruvate oxidase in the reduced state. The reduced concentration of α-oxoglutaric acid in vitamin B_{12} deficiency may be due partly to inadequate regeneration of intermediaries of the Krebs cycle. The cobamide coenzyme is required for the conversion of propionic to succinic acid via methyl malonyl coenzyme A (Marston *et al.* 1961). In vitamin B_{12} deficiency the metabolism of propionic acid is impaired (Marston *et al.* 1961) and the concentration of succinic acid falls (Smith & Monty 1959), and as a result the concentration of α-oxoglutaric acid and other intermediaries of the Krebs cycle may fall.

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The following paper was also read:

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