HÆMODYNAMIC STUDIES IN HIGH OUTPUT BERI-BERI

BY

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Despite the general belief that the cardiac output is high in heart failure due to thiamine deficiency, the evidence for this is chiefly clinical and the number of measurements reported is remarkably few. Using the ethyl iodide method of Henderson and Haggard (1925), Hayasaka and Inawashiro (1928) found that the cardiac output averaged 5.9 litres per square metre per minute at the "acme" and 4.5 litres on recovery. This confirmed the earlier work of Odaira (1925). Hayasaka and Inawashiro also reported that during treadmill exercise, sufficient to treble the oxygen consumption the cardiac output appeared to rise more in patients with beri-beri than it did in normal subjects and in the patients themselves on recovery. At rest the oxygen unsaturation of antecubital venous blood averaged 5.59 volumes per cent at the "acme" and 8.51 volumes per cent on recovery. During treadmill exercise the antecubital arteriovenous oxygen difference did not alter in the "acme," but increased to 13.0 volumes per cent on recovery. Weiss and Wilkins (1937) also found a narrowed femoral arteriovenous oxygen difference at rest in thirteen alcoholic cases. They showed that the decholin circulation time was accelerated, and from the clinical evidence of Wenckebach (1934) inferred that rice beri-beri and alcoholic beri-beri were functionally identical and characterized by generalized arteriolar dilatation. Porter and Downs (1942) used Grollman's acetylene method (1932) in two alcoholic patients given thiamine two and four days previously and the respective cardiac outputs were 4.71 and 9.80 l/min.

Burwell and Dexter (1947) were the first to determine the cardiac output at catheterization by collection of mixed venous blood and the use of the direct Fick principle. Their patients had a cardiac output of 11.7 litres per minute and manometric evidence of failure of both ventricles: the overall peripheral resistance was low. The findings a month later were normal. Later Lahey *et al.* (1953) reported one case and Iseri *et al.* (1954) three cases in which cardiac catheterization had been done. Lahey's patient had an output of 16.1 litres with normal filling pressures, while Iseri's three patients had outputs of 14.4, 8.3 and 11.4 litres per min. respectively, high venous pressures, and low peripheral resistances: some also had high pulmonary vascular pressures.

The total number of accurate measurements of cardiac output, therefore, amounts to five or possibly seven, if we include the two cases of Porter and Downs. Clearly the cardiac output in these cases was quite variable. In 1951 we realized that alcoholic beri-beri was not a rare disease in the principal cities of Australia. We have taken advantage of this situation to study the clinical features and the hæmodynamics in 19 cases with cardiovascular manifestations. The clinical features are being reported elsewhere; this paper concerns itself with the hæmodynamics and pathogenesis of the disease. All the patients were severe alcoholics; indeed, in this country cardiovascular beri-beri does not occur with alcoholic intakes below 1500 calories a day kept up for at least three months. Many of the present patients drank much more, but none of them had cirrhosis of the liver. Strangely enough it is not the rule to find cirrhosis in patients with classical cardiovascular beri-beri. The average age of the patients was 37 years, range 24 to 54.

This paper is concerned with classical high output beri-beri described so eloquently by Wenckebach (1934) and his pupil Aalsmeer (Aalsmeer and Wenckebach, 1929). This disease responds

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completely to thiamine, but merges almost imperceptibly into another disease, called alcoholic cardiomyopathy by Brigden (1957), which does not respond to thiamine. There the cardiac output is invariably low, due to irrecoverable muscle damage. Although we believe this low output syndrome to be, in fact, chronic beri-beri, failure to distinguish it from the classical syndrome has caused much confusion in the past twenty years.

The criteria we rely on for the diagnosis of classical beri-beri are as follows: (1) an adequate history of dietary deficiency, (2) complete recovery with thiamine, (3) co-existent neuritic beri-beri and (4) characteristic clinical features. The first two criteria are almost essential.

METHODS

Patients were studied in the basal state after an 18-hour fast. The catheterization procedure and the analytical methods have been described elsewhere (Blacket *et al.*, 1953). After duplicate determinations of cardiac output at rest, recumbent leg exercise was carried out in 6 patients and measurements were made during the second and third minutes.

Renal clearances of inulin and diodone were determined in five patients, either at a separate sitting or immediately after the cardiac catheterization. The procedure conformed to that described by Goldring and Chasis (1944) with the following modifications. With low rates of clearance the loading doses of inulin and diodone were reduced and the sustaining dose was given more slowly. Owing to the poor water diuresis in these patients three collection periods each of 20 minutes were used and the results averaged. Inulin was estimated by the method of Little (1949) and diodone by the method of Alpert (1941), acid cadmium sulphate being used for protein precipitation.

Forearm blood flow was measured by plethysmography in five patients (Barcroft and Swan, 1953); at least six inflow curves were obtained and the mean rate of flow computed. Plasma volume was determined with Evans Blue (Courtice and Gunton, 1949): plasma concentrations of the dye were determined at 10 and 15 minutes and extrapolated back to zero time. Blood pyruvate was determined by procedure B of Friedemann and Haugen (1943).

Heat elimination from the hand was measured with a modified Stewart calorimeter (Greenfield and Scarborough, 1949). A preliminary period of 20 to 30 minutes was allowed before readings were taken on a calibrated Beckmann thermometer set to read in the range 27° to 32° Centigrade.

FIG. 1.—Cardiac index and arteriovenous oxygen difference at rest before treatment (●) and after recovery (○). Isopleths of oxygen uptake are also shown.

FIG. 2.—Ventilation and cardiac index at rest before and after treatment.

TABLE I
HEMODYNAMIC DATA AT REST IN 16 PATIENTS WITH BERI-BERI, SOME STUDIED BEFORE AND AFTER TREATMENT.

Case	Age	Sex	B.S.A. sq. metres	Arterial blood % sat.	A-VO ₂ Diff- erence % sat.	Ventilation l./min.	O ₂ con- sump- tion ml. STP min./m ²	Cardiac index l./min./m ²	Pulse rate	Stroke vol. ml. min./m ²	Pressures (mm. Hg.)						Resistance dynes sec. cm. ⁻⁵		Work LV Work RV	P.C.V	Plasma vol.	Loss of weight with recovery (Kg.)
											P.C.	Pulm. Art.	Rt. vent.	Rt. auric	Brachial art.	System	Total	Art'lar				
											Abs.	Mean	Abs.	Mean	Abs.	Mean						
1	37	M	1.75	95	2.1	—	133	6.3	120	52.6	—	—	29/4	14	120/60	576	—	—	—	—	—	8.6
	13 days after thiamine		—	95	3.7	—	122	3.3	90	38.3	—	—	20/0	6	110/85	1268	—	—	—	—	—	—
2	25	M	1.71	87	1.0	5.1	155	15.5	88	176.0	20	40/26	30/21	25	—	100	—	30	8.0	—	—	8.6
	19 days after B ₁		—	97	4.5	3.1	125	2.8	80	34.5	—	20/8	12	20/1	140/80	1700	204	—	8.0	—	—	—
3	34	M	1.69	98	1.7	5.9	152	9.0	90	100.0	—	—	—	—	128/72	379	—	—	—	50	—	18.1
	3 days after B ₁		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4	35	M	1.78	95	3.5	5.4	147	4.2	88	47.2	—	47/25	37	—	145/80	896	400	—	4.4	45	5.32	11.3
	3 days after B ₁		—	98	3.5	4.9	143	4.1	95	43.2	10	41/13	25	35/2	172/86	1171	274	164	4.5	46	3.89	—
5	41	M	1.76	94	4.7	5.1	163	3.5	60	57.4	14	42/13	22	40/5	180/100	1664	288	105	7.0	54	—	5.0
	16 days after B ₁		—	94	4.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	65 days after B ₁		—	94	4.2	4.5	135	3.7	80	45.4	4	26/10	12	28/0	165/90	1450	150	90	—	55	—	—
	17 days after B ₁		—	94	4.2	4.1	128	3.0	90	33.9	1	16/4	10	20/0	125/95	1599	145	130	11.0	58	—	—
6	36	F	1.53	89	2.9	3.8	152	5.2	97	53.6	20	35/16	27	40/9	165/103	1199	270	200	5.0	46	3.40	8.6
	17 days after B ₁		—	95	4.1	4.4	146	3.6	68	51.6	—	15/3	6	18/2	145/92	1554	89	74	14.3	50	2.52	—
7	32	F	1.59	88	2.9	4.7	136	4.7	104	45.3	16	42/20	31	37/9	135/75	980	330	160	3.7	36	3.85	9.1
	12 days after B ₁		—	93	2.4	4.0	121	5.0	95	52.4	—	30/8	19	27/3	135/72	850	165	—	5.0	40	4.12	—
	33 days after B ₁		—	95	2.9	4.5	129	4.4	98	56.7	8	20/6	10	20/0	175/86	1059	96	20	10.2	42	3.64	2.3
	17 days after B ₁		—	95	3.1	4.5	130	4.3	100	43.3	4	17/6	10	20/0	170/98	1224	99	75	12.0	40	3.84	—
9	34	M	1.72	95	2.1	5.9	156	7.2	104	70.4	17	55/20	35	57/14	200/110	749	222	114	5.5	42	—	12.0
	17 days after B ₁		—	96	4.3	3.5	118	2.7	90	30.2	7	21/8	15	20/0	208/125	2584	292	136	9.7	—	—	—
10	30	M	1.86	90	2.1	7.2	175	8.4	123	68.8	14	57/27	37	60/11	130/83	97	443	188	3.3	50	3.45	3.2
	6 days after B ₁		—	94	4.5	4.5	145	3.3	95	33.9	5	48/15	25	48/1	130/86	108	332	266	4.1	48	3.31	—
11	24	M	2.10	91	3.6	4.1	171	4.7	90	52.3	22	57/26	35	58/15	195/105	863	283	149	5.2	—	—	26.3
	24 days after B ₁		—	96	4.2	3.5	120	2.9	88	38.1	1	15/5	9	16/2	126/78	94	1252	106	8.5	—	—	—
12	46	M	1.66	94	4.0	4.6	173	4.3	95	45.8	13	28/13	19	22/—	165/90	1110	221	67	4.9	32	4.47	5.4
	35 days after B ₁		—	95	5.3	4.8	136	2.6	110	23.5	5	25/8	13	30/3	—	—	242	149	—	38	3.80	—
13	31	M	1.72	94	2.2	3.8	155	7.0	84	83.7	21	40/24	31	40/15	130/75	90	528	205	3.6	44	4.01	10.0
	21 days after B ₁		—	93	2.8	—	108	3.8	58	38.4	7	24/10	14	24/5	140/80	100	1210	85	7.8	49	2.65	—
14	41	M	1.63	92	1.8	5.3	172	9.6	112	72.4	6	37/20	28	37/9	90/60	70	356	154	3.3	—	—	—
	28 days after B ₁		—	93	3.7	3.4	131	3.6	48	75.5	7	23/9	13	23/0	160/90	108	176	81	7.8	—	—	—
15	41	M	1.62	92	1.5	5.3	186	12.3	100	123.5	—	—	—	—	130/85	100	399	—	—	35	3.23	5.0
	16	M	—	90	3.9	—	196	—	70	—	—	36/10	16	36/3	150/64	90	1390	256	—	40	—	—

Duplicate determinations of cardiac output were made in all cases. Agreement between duplicates was better than 0.5 l/m²min. and the results from the first determination were used throughout

RESULTS

The results of cardiac catheterization at rest appear in Table I. The cardiac output varied between 7.2 and 26.5 litres a minute, the cardiac index between 4.2 and 15.5 litres (mean 7.12 litres/min.). The arteriovenous oxygen difference was low (mean 2.65, range 1.0–4.0 vols. per cent). Arterial oxygen unsaturation below 93 per cent occurred in Cases 2, 6, 7, 10, 11, 14, 15, and 16. The lowest saturation was 87 per cent in Case 2, who had the highest cardiac output in the series associated with a high pulmonary wedge pressure. There was, however, no correlation between flow over the whole range and arterial unsaturation. Most of those with cardiac indices above 8.0 litres a min. did show slight unsaturation. The reasons for this have not been determined.

The oxygen consumption tended to be high (mean 156 ml./m.²/min.) and to fall with recovery (mean 129 ml./m.²/min.). These relationships are shown graphically in Fig. 1. The resting minute volume of ventilation was 5.0 litres/m.²/min. and with recovery this fell to 4.1. As seen from Fig. 2 those with the highest cardiac indices tended to have the highest ventilatory volumes and these fell with recovery. Those with cardiac indices below 7 litres a minute had lower ventilatory volumes and showed no consistent change with recovery.

The pulse rate averaged 95 before treatment and 84 on recovery. There was no correlation between cardiac index and pulse rate; as seen from Fig. 3 the highest cardiac index of 15.5 litres a minute was achieved (in a digitalized subject) at a heart rate of 88. A second patient (Case 15) had a cardiac index of 12.3 at a heart rate of 100. The stroke indices varied accordingly. The mean stroke index was 102 ml./stroke/m.² at the first catheterization and 40 at the second.

FIG. 3.—Cardiac index and heart rate before and after treatment. Isopleths indicate stroke index.

FIG. 4.—Pulmonary capillary wedge pressure and cardiac index at rest. Poor correlation.

The pulmonary capillary wedge pressure varied from 6 to 22 mm. Hg, mean 16. On recovery the mean was 5. The wedge pressure had little relation to flow (Fig. 4) and an elevated pressure was taken as evidence of left ventricular failure.

The mean pulmonary artery pressure was also elevated, averaging 28 mm. Hg before treatment and 14 on recovery. As seen in Fig. 5 the height of the pressure bore no relation to flow. The mean PA–PC gradient was 13.2 mm. Hg and on recovery it showed an insignificant fall (mean 9.7). This was largely due to the large falls in Cases 9 and 14. The calculated pulmonary arteriolar resistance also showed no significant change with recovery. We conclude that the modest pulmonary

FIG. 5.—Mean pulmonary artery pressure (millimetres of mercury) at rest before treatment and after recovery.

FIG. 6.—Mean right atrial pressure and cardiac index at rest before treatment. Poor correlation.

hypertension seen in cardiovascular beri-beri is largely due to left ventricular insufficiency and only occasionally to increased flow.

The right ventricular end diastolic pressure varied from 0 to 21 mm. Hg and with one exception always fell with recovery. The right atrial pressure behaved similarly and fell from a mean of 9 to a mean of 0.25 mm. Hg on recovery. Like the left atrial pressure, the right atrial pressure bore no relation to the cardiac output (Fig. 6). Good examples of this are Case 15, where the cardiac output was 20.0 litres a minute and the right atrial pressure 4 mm. Hg, and Case 2 with a cardiac output of 26.5 (duplicate 22.5) and a filling pressure of 20 mm. Hg. Even when "normal" initially (<5), the right atrial pressure usually rose precipitously with exercise, confirming diminished right ventricular competence in all but the mildest examples of the disease.

The arterial pressure varied considerably with the severity and stage of the disease; a study such as this cannot be expected to portray these changes. However, the mean arterial pressure of the group averaged 102 mm. Hg at the first catheterization and 109 at the second. The figures for diastolic pressure were 82 and 90. These changes, although not great because of the inclusion of mild and treated cases, do reflect the tendency for the diastolic and mean arterial pressure to fall as the disease progresses. The mean systolic pressure did not change, being 147 in the first study and 148 in the second. This gives only a partial picture of the blood pressure changes, which have been described by Walters (1953) and will be discussed more fully elsewhere.

The calculated peripheral resistance tended to be low and always rose with recovery. In some the change was not great, but in others the resistance rose four or five times. The mean before treatment was 760 and on recovery 1495 dynes sec. cm.⁻⁵. Fig. 7 demonstrates the close negative correlation between flow and peripheral resistance.

Despite the hyperkinetic state, the work of the ventricles against resistance was the major factor in total ventricular work. For the right ventricle cardiac work rose as high as six times normal in severe cases; because of the fall in arterial pressure the rise for the left ventricle was less. The ratio of left to right ventricle work averaged 4.9 before treatment and 8.7 on recovery: it rose in every case (Fig. 8). This relative increase in right ventricular work is consistent with the dominance of the right side which was established pathologically and clinically by Wenckebach.

FIG. 7.—Cardiac index and total peripheral resistance plotted logarithmically. Good negative correlation.

The plasma volume was measured in 9 patients. In every patient with fluid retention it was high. As shown previously (Blacket, 1955), there was a remarkably close linear correlation between the fall in plasma volume and the loss of weight with recovery.

THE RESPONSE TO EXERCISE

The changes in ventilation, oxygen consumption, and various hæmodynamic parameters appear in Table II. They are best discussed in relation to the severity of the disease. Cases 8 and 16 were mild and had been given thiamine before the first study. Case 8 responded with a normal rise in cardiac output, an abnormal rise in right atrial and mean pulmonary artery pressure, and no change in stroke volume: ten days later a similar rise in cardiac output was achieved with no change in right atrial pressure. Case 16 studied 6 days after treatment had normal findings at rest, but exercise, which should have doubled the cardiac output, led only to a small rise and, as further indication of failure, a precipitous rise in right atrial pressure: the ventilatory response was also abnormal. Case 12 also was an example of mild beri-beri with peripheral neuritis and mild pitting œdema: the cardiac output rose normally on exercise, but the rise in pulmonary artery pressure was probably abnormal, from 19 to 31 mm. Hg.

Case 6 had a similar output at rest to Case 12, but both her pulmonary and right atrial pressures were abnormally high. Her response to very mild exercise was poor and her output scarcely rose at all: the pulmonary artery pressure rose and the stroke volume fell. On recovery more vigorous exercise produced a normal response.

TABLE II
DATA AT REST AND DURING EXERCISE IN 6 PATIENTS WITH BERI-BERI OF VARYING SEVERITY

Subject	State	Ventilation litres BTPS/min.	O ₂ con- sumption ml. STP	A-VO ₂ dif- ference vols. %	Cardiac out- put—l./min	Stroke volume	Pulse rate	Mean pressure (mm. Hg)	
								Pul. Art.	Rt. auric.
Case 2	Untreated Rest	8.7	265	1.0	26.5	301	88	30	20
	Exercise	23.5	558	2.2	25.4	242	105	40	25
	Treated Rest	5.3	213	4.5	4.7	59	80	20	0
	Exercise	10.2	489	6.0	8.2	—	—	—	0
Case 6	Untreated Rest	5.8	231	3.0	7.7	82	97	27	6
	Exercise	14.6	376	4.6	8.1	70	115	32	—
	Treated Rest	6.8	219	4.1	5.4	79	68	6	-1
	Exercise	14.6	456	5.6	8.1	81	100	9	0
Case 8	Treated 2 days Rest	7.5	226	2.4	9.3	98	95	19	1
	Exercise	13.1	432	3.7	11.6	100	115	26	6
	Treated 12 days Rest	8.4	242	3.1	7.8	100	78	10	0
	Exercise	13.3	443	4.4	10.7	111	96	15	0
Case 9	Untreated Rest	10.2	268	2.1	12.6	121	104	35	0
	Exercise	21.8	587	4.7	12.5	106	118	55	10
	Treated Rest	6.1	203	4.3	4.7	52	90	15	0
	Exercise	8.6	520	5.9	8.8	80	110	25	4
Case 12	Untreated Rest	7.7	288	4.0	7.2	76	95	19	-1
	Exercise	15.4	543	5.6	10.0	88	113	31	—
Case 16	Treated 6 days Rest	7.2	196	3.9	5.0	71	70	16	3
	Exercise	18.4	590	9.2	6.4	64	100	—	16

Note that data have not been corrected for body surface

Case 2 and Case 9 were examples of more severe beri-beri with resting outputs of 26.5 and 12.6 litres a minute respectively. Neither of them showed any significant change in output during exercise. Both of them showed a fall in stroke volume, tachycardia, and a rise in right atrial and pulmonary artery pressures. In Case 2 the response to exercise 19 days later was normal, but Case 9 still showed marginal rises in pulmonary artery, right atrial, and pulmonary wedge pressures 17 days after the first catheterization.

In addition to the six patients listed, exercise was also carried out at the second catheterization in Cases 11, 13, and 15 at the 24th, 21st, and 28th day after thiamine respectively: the findings were entirely normal. In view of the old idea that cardiac "irritability" with prolonged tachycardia after exercise frequently persists in convalescence, it should be emphasized that none of these patients showed this phenomenon.

FIG. 8.—Work of left ventricle against resistance (W_{LV}) over work of right ventricle against resistance (W_{RV}) plotted against cardiac index before and after treatment. The work ratio rises with recovery.

FIG. 9.—Ventilation and oxygen consumption at rest ($\circ$) and during exercise ($\bullet$) in 6 patients with cardiovascular beri-beri. In order to compare the response with the normal regression line (---) from Holland and Blacket (1958), the data have not been corrected for body surface area. Moderate hyperventilation occurs on exercise.

The ventilatory response to exercise is shown in Fig. 9, where the slope for each patient can be compared with the normal regression line obtained in healthy young subjects in this laboratory (Holland and Blacket, 1958). Cases 8, 12, and 16 with mild beri-beri and the lowest pulmonary artery pressures responded normally, but at a slightly higher level, than the normal subjects. Cases 2, 6, and 9 with higher pulmonary vascular pressures and more severe disease responded abnormally.

In summary the circulatory and ventilatory response to exercise in cardiovascular beri-beri is similar to that found in the common forms of heart disease. Mild cases show a normal or reduced output response with an abnormal rise in pulmonary and right atrial pressures. With severe disease the cardiac output remains fixed, the stroke volume falls and the pressures go higher.

THE MUSCLES

The results so far confirm the work of earlier workers that there is an overall vasodilatation in beri-beri with a fall in total peripheral resistance. Although neither they nor subsequent workers measured muscle blood flow, Aalsmeer and Wenckebach thought that the peripheral arteriovenous shunt occurred in the muscles (Wenckebach, 1934). Aalsmeer had found that adrenaline raised the venous pressure and lowered the diastolic pressure, while Wenckebach showed that pitressin had opposite effects. Both these findings were compatible with the known actions of these drugs on the muscles. Weiss and Wilkins (1937) also found a low femoral arteriovenous oxygen difference.

Forearm blood flow was measured by plethysmography in five patients. The results appear in Table III and Fig. 10. All of these subjects had florid beri-beri and the catheterization data for Cases 14 and 15 appear in Table I. Case 14 was studied one day after catheterization and after giving thiamine. Case 15 was also studied the day after catheterization, but no thiamine had been given. Case 17 had acute pernicious beri-beri on admission with a hyperdynamic circulation and severe metabolic acidosis: he also was studied 24 hours after thiamine. Case 18 was a moderate example of the disease with raised venous pressure, pistol-shot sounds, and an easily appreciated hyper-dynamic circulation. His output was probably in the 10–12 litres a minute range and he was studied untreated. Case 19 was more severe and was on the verge of an acute pernicious termination

TABLE III

FOREARM BLOOD FLOW (F.B.F.) IN FIVE PATIENTS MEASURED BY VENOUS OCCLUSION PLETHYSMOGRAPHY

Subject	Conditions	F.B.F. ml./100 ml./ min.	Pulse rate	Blood pressure
Case 14 11/3/54	Room Temp. (R.T.)= 24° C. 24 hours after thiamine	6.7	75	110/60
15/3/54	R.T.=24°	2.4	43	145/85
Case 15 5/8/54	Untreated R.T.=19°	8.0 8.3	100	135/80
	R.T.=24°	7.9	105	135/80
9/8/54	R.T.=16° R.T.=27° Footbath 40°. Sweating	6.5 8.5	85 90	150/80 150/75
11/8/54	R.T.=25° Control L. noradrenaline 19 µg./ min. intravenous Recovery	6.5 4.9 5.9	83 79 85	150/95 190/112 150/95
18/8/54	10 mg. thiamine daily since 11/8/54 R.T.=25°	2.5	80	160/100
Case 17 15/2/55	1 day after thiamine R.T.=28°	8.7	94	140/70
17/2/55	R.T.=28°	4.6	75	170/80
23/2/55	R.T.=25°	1.8	70	150/90
Case 18 23/3/55	Untreated R.T.=25°	8.7	100	143/81
30/3/55	R.T.=27.4	4.1	70	110/86
Case 19 4/7/57	Treated 1 day R.T.=24°	11.3	82	125/75
22/7/57	R.T.=24°	3.0	88	145/91

to the disease, when admitted one afternoon. During the night his systolic pressure fell to 80 and he was given thiamine and studied the next morning. In computing the flow per 100 ml. of forearm, we have used the "dry" volume of the limb rather than the "wet" volume, when œdema was present. The same segment of limb was used on each occasion.

The results show that forearm flow is high in beri-beri, and falls with recovery. Forearm flow correlated roughly with the clinical severity of the disease. Thus Cases 17 and 19 with acute pernicious beri-beri, studied after thiamine, showed flows between 3 and 5 times the "recovery" value. Cases 14 and 15, who were less severe, had flows roughly three times the control values and Case 18, who was clinically the least severe of the five, had the lowest relative increase at the height of his disease. Return to normal occurred in three or four days in Cases 14 and 17 after thiamine was given. As controls for these observations measurements were made on three

patients with low output failure due to rheumatic heart disease. The flows were 1.9, 1.3, and 1.2 ml. per 100 ml. respectively.

Forearm flow reflects only partially muscle flow, since bone flow and skin flow also contribute to the total. As shown below, the blood flow to the hand is reduced in beri-beri with heart failure, but we have no data on flow to the skin or to the bone of the forearm. In Case 15 it was of interest to find that reflex vasodilatation, which raised hand flow from 0.9 to 3.0 ml./100 ml./minute, raised forearm flow by a similar amount, while noradrenaline lowered forearm flow but not to normal. Clinically the skin of the forearm is much warmer than that of the hands, but the meagre results we have do not allow of any partitioning of the increase in forearm flow between muscle and skin. We suspect that true muscle flow is probably raised by rather more than the results of forearm plethysmography suggest.

FIG. 10.—Forearm blood flow before treatment and after recovery in five patients. The normal range is enclosed in the rectangle. The forearm flow is high in the untreated disease.

FIG. 11.—Heat elimination from the hand under nearly standard conditions before treatment and after recovery in four patients. Normal range enclosed. The heat elimination (and hand flow) are low in untreated beri-beri.

HAND FLOW AND SKIN TEMPERATURE

Weiss and Wilkins (1937) wrote that the "skin was often flushed and warm" and Wenckebach (1934) noted capillary pulsation in the finger tips in some cases. Table IV and Fig. 11 show the heat elimination in four patients as measured in the calorimeter. These cases represent both moderate and severe, but not moribund, examples of the disease. In all four patients the heat elimination under standard conditions before treatment was low and under similar conditions became much higher with recovery. The low heat elimination (and by inference, hand flow) in Cases 18 and 19 contrasts strikingly with the high forearm flows described above.

TABLE IV
THE HEAT ELIMINATION (H.E.) FROM THE HAND IN FOUR PATIENTS WITH BERI-BERI

Subject	Condition	Room temp	Pulse	Blood pressure	H.E. cal./min.	H.E cal./100 ml./min.
Case 4 Untreated 25/10/51	At room temp. ..	23.3	82	148/85	19.6	4.5
	Reflex vasodilatation, sweating	23.4	85	145/80	179.5	41.3
Case 7 Untreated 6/5/52	At room temp. ..	22.0	102	135/80	27.0	7.9
	Reflex vasodilatation, sweating, light-headed	22.0	106	135/78	266.9	78.2
Treated 9 days 15/5/52	At room temp. ..	23.4	81	114/76	55.9	19.0
	Reflex vasodilatation, sweating	23.4	94	112/72	259.8	88.4
Case 18 Untreated 23/3/55	At room temp. ..	26.4	100	143/81	42.2	11.4
	Reflex vasodilatation, sweating	33.8	109	139/73	239.1	64.6
Treated 3 days 30/3/55	At room temp. ..	27.4	116	110/86	146.1	39.5
	Reflex vasodilatation, sweating	30.3	128	101/76	208.3	56.3
Case 19 Treated 1 day 4/7/57	At room temp. ..	24.0	82	126/75	20.9	6.4
Treated 18 days	At room temp. ..	24.0	88	145/91	168.2	46.7

Cases 4 and 7 were examples of moderate disease with relatively low cardiac outputs and considerable heart failure. Cases 18 and 19 had more florid beri-beri with cardiac outputs in the 12–15 litres a minute range. Reflex vasodilatation was achieved by immersion of the feet in water at 44° C.

In Case 15 the hand flow measured by plethysmography on 5/8/54, when the forearm flow was measured, was 2.8/ml./100 ml./min. From the data of Cooper *et al.* (1949) the hand flow was low and of the same order as in the cases studied by calorimetry. The nail beds were cyanosed. Again there was a marked contrast with the high forearm flow (Table III) and a striking difference in the temperature of the forearms and hands.

The response to reflex vasodilatation (Lewis and Pickering, 1931) was greatly delayed but ultimately satisfactory in Cases 4 and 7. In Case 18 the rise in heat elimination on both occasions was extremely slow. The environmental temperature was therefore raised and some vasodilatation occurred. However, the hand not in the calorimeter remained cold, when all the observers were sweating profusely. Similarly in Case 15, studied by plethysmography, we were unable to abolish the cyanosis of the nail beds by reflex vasodilatation, before the patient himself terminated the experiment.

The results leave little doubt that the hand does not share in the vasodilatation demonstrated in the muscles. The circulation in the hand behaves as it does in low output failure (Burch, 1954). In normal subjects reflex heating abolishes sympathetic tone. The extraordinary resistance of vasoconstriction to prolonged body heating in two of our cases with high outputs raises the question of non-nervous factors. The effect of nerve block has not been tried.

RENAL HÆMODYNAMICS

Glomerular filtration rate (inulin clearance) and renal plasma flow (diodone clearance) in five patients are shown in Table V and Fig. 12. Renal vasoconstriction of similar order was present

in every case. The cardiac outputs varied from 7.4 to 20.0 litres a minute in these same untreated cases and clearly there was no correlation between the cardiac output and renal flow patterns. Nor was there any correlation with right atrial pressure or mean arterial pressure. The filtration fraction was high, averaging 0.25.

The findings in Case 15 were extremely interesting in that the cardiac output was very high and right atrial and systemic pressure were virtually normal, while the renal plasma flow was about one-third of normal: the hands were also cyanosed and cold due to vasoconstriction. At rest there was no clinical evidence of general circulatory embarrassment and the heart was only slightly dilated (cardio-thoracic ratio 0.49). Clearly the dilatation seen in this man's forearm (Table III) was regional, and vasoconstriction in kidneys and hands appeared to be a homeostatic mechanism aimed at preservation of the blood pressure. Lahey *et al.* (1953) described a similar case and also noted inhibition of water diuresis, which we observed but did not measure.

TABLE V
GLOMERULAR FILTRATION RATE, RENAL PLASMA FLOW, FILTRATION FRACTION, AND PACKED CELL VOLUME IN FIVE PATIENTS WITH BERI-BERI

Subject	State	G.F.R. ml./min.	R.P.F. ml./min.	F.F.	P.C.V.	Blood urea mg. %	Cardiac output l./min.
Case 4	Untreated	68	308	0.22	46.0	70	7.4
Case 5	Treated 4 days	67	252	0.27	53.9	41	6.1
	19 days	83	562	0.15	54.8	—	6.4
	65 days	101	520	0.19	48.0	—	5.5
Case 6	Untreated	77	292	0.27	46.0	—	8.0
	Treated 19 days	96	677	0.14	50.1	—	5.4
Case 9	Untreated	61	268	0.23	42.3	—	12.6
Case 15	Untreated	70	207	0.33	34.8	21	20.0
Means	Untreated	68	269	0.25			

Case 5 shows that renal vasoconstriction may be slow to relax and diuresis may also take many days to reach its maximum. Indeed the blood urea may go on rising for some days after treatment begins.

These findings are similar to those of Lahey *et al.* (1953, one case) and Iseri *et al.* (1954, two cases). Iseri's third patient had complicating pneumonia and was studied the day his temperature became normal: the renal plasma flow was normal and glomerular filtration rate *above* normal. Except for this patient, all reported cases show that the kidney, like the skin of the hand, does not share in the general vasodilatation.

The extent of the reduction in renal plasma flow and filtration rate in these and other reported cases is not to be taken as the maximum that can occur in beri-beri. As shown elsewhere (Blacket, 1955) the fall in blood pressure that marks the onset of acute pernicious beri-beri is associated with oliguria and anuria. Following restoration of the circulation with thiamine, the blood urea has been found to rise in these severe cases, and the urine flow to remain low for two days or even longer. Although inulin and diodone clearances have not been measured in such cases, it is safe to assume that they are very low indeed.

HEPATIC BLOOD FLOW

Hepatic flow by the bromsulphthalein method (Bradley *et al.* 1945) was estimated in two patients only. The first (Case 7) had a cardiac output of only 7.5 litres per min. and duplicate hepatic flows of 1528 and 1603 ml. a minute. In the second the cardiac output was not measured, but he

had a forearm flow of 11.3 ml./100 ml./min. (Case 19, Table III) and can be presumed to have had moderately severe beri-beri: he did in fact have marked oliguria and his hepatic flow was 2440 ml. a minute.

These two cases need supplementing, but they do show that in beri-beri, unlike low output failure (Myers and Hickam, 1948), the hepatic flow is normal or high. It does not appear to rise as much as the muscle flow, but further observations are necessary.

METABOLIC FACTORS IN BERI-BERI

In mild and moderate beri-beri we have confirmed earlier work that the plasma bicarbonate is normal or slightly reduced (Inawashiro and Hayasaka, 1928). In addition, plasma sodium, potassium, chloride, and pH showed no consistent change. The blood pyruvate also was not much raised and Lu (1939) found that it became normal long before the pulse rate. In balance studies on three patients with moderate beri-beri, Iseri *et al.* (1954) found during recovery a positive potassium balance (329 m. equiv. in one case) and a much larger negative sodium balance depending on the extent of fluid retention.

FIG. 12.—Renal plasma flow (diodone clearance) before and after treatment. Normal range enclosed. Renal plasma flow (and glomerular filtration rate) are reduced in beri-beri.

FIG. 13.—Blood pyruvate after ingestion of glucose (1.75 g./kilo at G in Cases 15 (●) and 14 (○). At E Case 15 walked up and down 60 stairs at a slow rate. Note the large rise from exercise.

In acute pernicious beri-beri Lu and Platt (1939) found marked elevation of pyruvate. Fig. 13 shows the blood pyruvate in Cases 14 and 15, both of whom had severe beri-beri just short of acute pernicious disease. In both the resting levels were high. The injection of glucose had very little effect on blood pyruvate in Case 14. In Case 15, therefore, exercise (climbing 60 stairs) was carried out two hours after the glucose ingestion. As it happened, the blood pyruvate level did rise after glucose alone, but reached much higher levels immediately after the exercise.

We have found no reported reference to plasma bicarbonate levels in acute pernicious beri-beri. In Case 10, who was admitted moribund and given thiamine immediately, the plasma CO_2 combining power six hours later was 6.3 m. equiv. per litre. Nine hours after admission it was 21.2. Three other cases, all seen after thiamine had been given, had CO_2 combining powers of 9.0, 12.5, and 13 m. equiv. per litre. Although these figures are lower than is usual in low output failure (Peters *et al.*, 1927; Fraser *et al.*, 1928), they are higher than in severe diabetic acidosis. No measurements of pH were made.

DISCUSSION

The results show that the cardiac output in beri-beri is extremely variable, ranging from a high normal to twenty litres a minute or more. Such high flows have not been reported previously in beri-beri or indeed in any other high output state. The variability of the flow from case to case is in accord with the few accurate determinations referred to previously. Although the oxygen consumption may be high and so demand an increased blood flow, this is not an important factor in determining the high cardiac output. The circulation time is greatly reduced and the overall arteriovenous oxygen difference may be as low as 1 volume per 100 ml. This implies an overall vasodilatation, which is confirmed by the low peripheral resistance. The negative correlation between cardiac output and mean arterial pressure in this series was close and it is probable that the high flow is determined by the low peripheral resistance. The alternative possibility that the high cardiac output is primary was accepted when it was thought that vagal degeneration was responsible for tachycardia. Wenckebach rejected this explanation and the present work confirms that tachycardia is less important than an increased stroke volume in the high cardiac output. Indeed the highest flow in the present series was achieved at a heart rate of only 88 a minute, with a stroke volume of 301 ml. per beat. This is in agreement with the finding of Bishop, Donald, and Wade (1955) that the "keystone of the hyperkinetic state is an increase in stroke volume, rather than an increased heart rate."

The high stroke volumes achieved in our most florid cases of beri-beri at rest are higher than in other hyperkinetic states and may be even twice as high as in vigorous muscular exercise in normal subjects (Asmussen and Nielsen, 1955). The resting cardiac output in some of our subjects corresponded to that found in muscular exercise at an oxygen consumption of 2.5 litres a minute, which for an untrained subject is extremely hard work. This may go on for several days at least and it is not surprising that it leads to cardiac failure. Despite this ultimate failure, the thiamine deficient myocardium performs remarkably well.

The plethysmographic studies show that the low peripheral resistance is due principally to vasodilatation in muscle—in effect an arterio-venous fistula. This vasodilatation has been demonstrated in cases without clinical evidence of heart failure. Indeed one consequence of vasodilatation—muscle swelling—has long been recognized as one of the earliest signs of beri-beri (Reinhardt, 1916). This is in conformity with the biochemical evidence that thiamine is concerned in carbohydrate metabolism which is intimately connected with working muscles. It appears that the block in the metabolic pathways, induced by thiamine lack, leads to arteriolar dilatation. This appears to be the first hæmodynamic aberration, for in mild and even moderate beri-beri cardiac performance often remains adequate at rest. The meagre data we have collected on exercise in recovering patients do not help in deciding whether exercise performance is normal in ingravescient illness, for the myocardium itself may change as a result of continued thiamine deficiency.

Muscular vasodilatation increases the venous return and according to the concepts of Krogh (1912) and Patterson, Piper, and Starling (1914) this increases the cardiac output, up to a maximum of about 25 litres a minute. However, the increased arteriolar run-off from the muscles brings about other changes. It has been shown in dogs that opening an arteriovenous fistula leads to body vasoconstriction (Van Loo and Heringham, 1949; Frank *et al.*, 1955). With fistulæ accommodating less than 20 per cent of the control cardiac output, the cardiac output increased by the full amount of the fistula flow and vasoconstriction did not occur. With larger fistulæ the body flow

fell and the cardiac output rose less than expected. Vasoconstriction maintained the mean arterial pressure until fistula flow reached 60 per cent of the control total output. Beyond that the arterial pressure fell. With fistula flows exceeding 60 per cent of the control output, acute increases of plasma volume with saline led to an increase of cardiac output to the full extent of the fistula flow and a disappearance of body vasoconstriction. Hilton *et al.* (1955) in the same experiments also showed that body vasoconstriction involved the kidneys. There was a reduction in glomerular filtration rate, a greater reduction in renal plasma flow, and an increase in the filtration fraction. Similar changes were present in our patients with beri-beri, probably for similar reasons.

In view of the emphasis in modern texts on the warmth of the hands in this and other high output states the finding of a low heat elimination relatively resistant to reflex vasodilatation is of interest. Vasoconstriction also occurs in the hand at the onset of muscular exercise, but gives way to dilatation after a few minutes in order to regulate temperature (Christensen and Nielsen, 1942). Vasoconstriction also occurs in the skin and perhaps the muscles of the arm when the legs are exercised (Donald *et al.*, 1955). This is more pronounced in patients with an impaired cardiac output response to exercise. Our findings in beri-beri therefore agree with the general thesis that an increased demand for blood by the muscles or an obligatory increase in muscle flow due to thiamine deficiency leads to cutaneous vasoconstriction.

The apparent discrepancy between the capillary pulsation with warm hands described by Wenckebach and the cyanosed cold hands seen by us may be explained by the fact that all our patients had evidence of circulatory insufficiency. In the early stages of beri-beri, when alcoholics do not come to a hospital, an increased hand flow may well be present. When the disease is producing disability the finding of cold or cyanosed hands should not prejudice the diagnosis of beri-beri.

This cutaneous vasoconstriction appears to be an extremely sensitive index of circulatory insufficiency. It has been demonstrated in patients with right atrial pressures that are in the normal range and with normal mean systemic blood pressure. Similarly in the fistula experiments discussed above, body vasoconstriction occurred with insignificant changes in right atrial and arterial pressure. Nonetheless the filling pressure in our cases was probably abnormal as it fell with recovery and rose with exercise.

The finding, in the only two patients studied, that splanchnic blood flow was elevated suggests that thiamine deficiency also leads to vasodilatation in the liver. Quantitatively it seems to be less striking than in the muscles, but a study of more florid cases with higher cardiac outputs is desirable. The high liver blood flow contrasts with the low flows found in low output failure (Myers and Hickam, 1948) and with the fall during exercise in both normal subjects (Wade *et al.*, 1956) and in patients with chronic rheumatic heart disease (Bishop *et al.*, 1955b).

Pulmonary arterial pressures at rest in those who had cardiac indices below 8 litres a minute usually exceeded those obtained by Dexter *et al.* (1951) and Donald *et al.* (1955) in exercising normal subjects. At flows exceeding 8 litres a minute per square metre, pulmonary arterial pressures in these patients were of the same order as those found by Donald at comparable flows during exercise. Unfortunately Donald did not measure wedge pressures which in this series were usually raised.

Also in agreement with both groups we found no significant change in pulmonary vascular resistance during the high output state. The pulmonary artery to capillary gradient tended to be higher with increasing flows but there were considerable variations. Dexter too found an increasing gradient with increasing flows during muscular exercise. It was of great interest to find in our Case 10 that reduction of flow from 15.7 to 6.0 litres a minute was associated with a marked rise in pulmonary arteriolar resistance and a fall in pulmonary wedge pressure. This patient had much right ventricular hypertrophy by electrocardiogram (unusual in beri-beri) and it is tempting to infer that pulmonary vasoconstriction was induced reflexly as a brake on the hypertrophied right ventricle.

On exercise the rise of mean pulmonary arterial pressure tended to be higher than in Dexter's normal subjects and in the subjects themselves on recovery. This we interpret as evidence of left ventricular failure.

Elevation of right and left atrial pressures in most patients with beri-beri contrasts with the findings in other hyperkinetic states (Bishop *et al.*, 1955b) and supports the idea that raised filling pressure is a sign of myocardial insufficiency. An increased venous return stimulates the ventricle but ventricular compensation should be complete so that atrial pressure remains normal. Failure to achieve a normal filling pressure must mean cardiac insufficiency.

Doubtless because of this factor we have not seen in this form of hyperkinæmia the super-normal cardiac outputs found by Bishop and his colleagues in anæmia, and by Hayasaka and Inawashiro in beri-beri. From the meagre data the Japanese workers gave, it appears that most of their subjects had mild cardiovascular beri-beri. Their findings need confirmation, but are in line with those reported by Bishop in anæmia.

The variation in ventricular dynamics from case to case deserves emphasis. Fig. 6 shows a wide range of output at any given filling pressure. No single Starling curve could be fitted to the data, whether we used total flow, stroke volume, or work per beat as the abscissa. Severe beri-beri as judged by high pyruvate levels, metabolic acidosis, hyperpnœa, and a high cardiac output is not incompatible with normal filling pressures at rest. In other cases without acidosis, the flow is little above normal but the filling pressure is most abnormal. Between these two extremes almost any combination of flow and filling pressure occurs. Wenckebach attributed heart failure in beri-beri to "weakness of the muscle and loss of tone of the myocardium, which comes about through an overflow from the veins, due to insufficiency of the arterial part of the peripheral system." (free translation from Wenckebach, 1934).

Though this is the essence of the more florid cases, Keefer (1930) pointed out that many cases seen in Peking had little clinical evidence of a hyperdynamic circulation. Keefer's cases were probably similar to some of our own with relatively low outputs. They show that cardiac dysfunction is not necessarily due to overfilling but to primary myocardial dysfunction. This dysfunction is probably metabolic in part for very high filling pressures with low "high outputs" may return to normal in a few days with thiamine. But there is much evidence in man that histological changes also occur (Weiss, and Wilkins, 1937; Crawford, 1952) although they may be non-specific. The frequent slow return of cardiac size to normal and the persistence or worsening of S-T segment changes in the electrocardiogram for as long as six weeks after therapy support this conclusion. Indeed it is probable that the syndrome of alcoholic cardiomyopathy (Dock, 1940; Brigden, 1957), which occurs in the same setting as classical beri-beri, represents nothing more than failure of resolution and organization of muscle necrosis and interstitial œdema that occur acutely. The passage from classical recoverable beri-beri to chronic thiamine-resistant myopathy had been observed in several patients (Conomy, 1959). Low grade thiamine deficiency may produce minimal symptoms, which are accepted by an alcoholic as part of his life. Going on for years, continued deficiency may well end in severe fibrosis (Schlesinger and Benchimol, 1951) without any clinical episode of florid beri-beri.

Since the work of Weiss and Wilkins (1937) there has been considerable controversy over the importance of left as opposed to right ventricular failure. Wenckebach (1928, 1934) and Vedder (1938) emphasized the importance of right ventricular hypertrophy, dilatation, and failure, but recognized that the left ventricle might show these changes in lesser degree. Weiss and Wilkins thought that left-sided failure was just as common as right. Fig. 14 shows that pulmonary wedge pressure and right atrial pressure usually rise together. In this sense Weiss and Wilkins were correct. But the wedge pressure is usually below the critical level for pulmonary œdema, which in our experience is minimal or absent in the great majority. Matsuoka (1915) also found pathologically that pulmonary œdema was less than in the more common varieties of left ventricular failure. Pulmonary œdema may be a feature of the terminal illness, particularly in those with the lower flows. We have not seen it in isolation without commensurate right ventricular failure.

The left ventricle carries the same volume load as the right, but the more florid the case the lower the resistance that opposes it. The right ventricle, however, contracts against the resistance of the pulmonary circuit, which may rise a little, and of the left ventricle, which may be as much as four

times normal. Fig. 8 shows the change in the ratio of left ventricular to right ventricular work against resistance in 9 cases. Although there is considerable variation all cases showed a rise in the ratio with recovery, some by a factor of 3. The absolute increase in left ventricular work in florid cases may be by a factor of 4. The work of both ventricles is clearly much increased but that of the right increases more than that of the left.

The present findings therefore confirm the classical view that right ventricular failure is dominant, but they also show that the left ventricle may suffer considerably, particularly when its performance is impaired by metabolic and structural changes of thiamine deficiency.

The importance of metabolic acidosis in beri-beri cannot be decided from the limited observations we have made. It has been shown (Lange *et al.*, 1951) that severe acidosis induced in dogs by infusions of gluconic acid will increase the cardiac output by 142 to 381 per cent when the *pH* is reduced by about 0.3 units. This increase in output is associated with bradycardia and an increased stroke volume. Whether such severe acidosis occurs in acute pernicious beri-beri remains unknown. Such patients do have deep rapid respiration as in diabetic acidosis, and it is quite likely from the bicarbonate levels that *pH* changes approaching those in diabetic coma do occur. However, in diabetic acidosis Howarth *et al.* (1948) found that restoration of the alkali reserve did not affect the vasodilation, low blood pressure, and slightly raised cardiac output. They thought that peripheral vasodilatation was present in the muscles, but as in beri-beri the factor responsible for this is unknown.

Metabolic acidosis with further vasodilatation and sinus deceleration may prove to be the last straw in pernicious beri-beri. But it is quickly overcome by thiamine, and in moribund cases with a low output and absent peripheral pulses, the cardiac output rises to high levels as the plasma bicarbonate returns to normal. Case 10, in which the output was determined 24 hours after thiamine, is our best documented example of this. Acidosis clearly is not responsible for the high flow seen in the usual case. The metabolic aberration responsible for vasodilatation in the muscles is more slowly overcome and usually takes two or more days to right itself. In diagnosis the low plasma bicarbonate may prove useful.

Weiss and Wilkins attributed the beneficial effect of thiamine to the closing down of peripheral arteriovenous shunts. Lahey *et al.* (1953) confirmed this by demonstrating a reduction in cardiac output with a rise in peripheral resistance within two hours after giving thiamine. But in their case the right atrial pressure was normal and did not change after thiamine. The possibility that thiamine

FIG. 14.—Right atrial and left atrial (pulmonary capillary) mean pressure (millimetres of mercury) at rest in untreated cases. The filling pressures of the two ventricles rise together.

FIG. 15.—Loss of weight and fall in plasma volume with recovery in 9 patients with beri-beri. Data for 4 of these are from patients not listed in Table I. The units have been changed and an error corrected from a previous publication (Blacket, 1955). Fluid retained in beri-beri is distributed in constant proportion between intra- and extra-vascular spaces.

has a direct myocardial action by correcting myocardial metabolism has not been ruled out. In Case 4 right atrial pressure fell in 3 days from 19 to 3 mm. Hg with little change in flow or resistance.

In one patient 1.5 mg. of digoxin given intravenously produced no hæmodynamic response in two hours. Clinically we have seen some resolution of œdema after digoxin and have never seen it do harm as is sometimes claimed.

Finally, beri-beri provides an example of a rapidly reversible form of heart failure in which fluid retention is often conspicuous. Fig. 15 from an earlier paper (Blacket, 1955) shows that the losses of weight and plasma volume with recovery are linearly related. This finding agrees with that of Funkhouser *et al.* (1957) in low output failure and therefore suggests that similar factors are operative. However, as Manson (1900) recognized and we have confirmed, the œdema of beri-beri is not necessarily cardiac in distribution. Any generalizations should be avoided at present, particularly as earlier workers, admittedly using less accurate criteria than Funkhouser *et al.*, have not found the same linearity (Gibson and Evans, 1937; Meneely and Kaltreider, 1943; Gunton and Paul, 1955). From the experiments of Frank *et al.* (1955) plasma expansion probably helps to maintain the cardiac output in beri-beri for a time. If excessive, however, it becomes a liability, for venesection has a favourable, but transient, effect on the symptoms of acute pernicious disease (Wenckebach, 1934).

SUMMARY

Various hæmodynamic observations have been made in 19 patients with thiamine-sensitive alcoholic beri-beri. They show that the cardiac output and ventricular filling pressures are extremely variable. The cardiac output at rest varies from a high normal to about 25 litres a minute, and the right atrial pressure from normal to 20 mm. Hg. There is no correlation between pressure and flow, and it is concluded that myocardial performance varies tremendously from case to case.

Filling pressures on the two sides of the heart tend to rise together. The work of both ventricles is increased, but that of the right rises more than that of the left. This is in conformity with the classical view that right-sided failure is dominant.

The total peripheral resistance falls in beri-beri to as low as a quarter of normal in the most florid cases. This fall in overall resistance is due principally to vasodilatation in the arterioles of the somatic musculature, where there is in effect an arterio-venous fistula. There is a simultaneous rise in resistance to flow in the skin of the hand and in the kidneys. This is interpreted as a homeostatic reflex vasoconstriction, aimed probably at maintenance of a normal arterial pressure.

The plasma volume tends to expand in beri-beri according to the availability of fluid. This expansion exceeds physiological requirements in many cases and accentuates circulatory embarrassment. There is a linear relationship between plasma volume expansion and gain in weight due to œdema.

In acute pernicious beri-beri there is a severe metabolic acidosis and this, superimposed on the hyperkinetic state, may be the final cause of death.

It is suggested that thiamine deficiency has its main circulatory effects on the arterioles of the muscles but, sooner or later in different cases, impairs myocardial performance directly. The clinical picture is determined by the preponderance of one or other of these factors, complicated by varying amounts of fluid retention and in acute pernicious beri-beri by a terminal acidosis.

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