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Biochemical changes associated with the use of haemodilution with 5% dextrose in water and mannitol for open-heart surgery

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Many advantages are gained from the use of haemodilution in open-heart surgery. There is a lessened post-operative morbidity from bleeding, renal failure, and serum hepatitis. However, dilution with 5% dextrose in water is associated with a greater metabolic acidosis and a higher incidence of serious dysrhythmias than is pure blood. In order to elucidate the causes of these complications, 26 patients were studied using different degrees of haemodilution. The metabolic acidosis appeared to be mainly due to the dilution of blood buffer. Changes in electrolyte balance were more marked with greater dilution. The effects on serum sodium and chlorides were transient. The serum potassium level fell markedly during the post-operative phase and was associated with dysrhythmias. We believe that variation in potassium concentration is due to redistribution of potassium between the intracellular and extracellular phase as well as to an increased urinary excretion of potassium. The acidosis and hypokalaemia can be rapidly corrected by the administration of sodium bicarbonate and potassium. The changes in acid-base metabolism and electrolyte balance can possibly be prevented by suitably modifying the priming fluid.

The massive quantities of blood used during open-heart operations may cause complications unrelated to the actual surgery. Serum hepatitis occurs in direct proportion to the quantity of blood given; a case incidence of 0·6% per bottle of blood has been reported by Alsever and Barger (1961). Occult incompatibility reactions can occur in spite of meticulous cross matching and proved *in vitro* compatibility (Fudenberg and Allen, 1957; Allison and Blumberg, 1961). Schmidt, Peden, Brecher, and Baranovsky (1961) and Krevans, Jackson, Conley, and Hartmann (1957) have shown that with the use of pure blood primes the early disruption of platelets may cause post-operative bleeding.

Diluted blood-priming solutions were first introduced by Zuhdi, McCollough, Carey, and Greer in 1961. By 1962 Cooley, Beall, and Grondin had already gained an extensive experience of this technique which they believed reduced the complications of bypass perfusions. It is now claimed that haemodilution affords protection against renal failure (Norman, McDonald, and Sloan, 1964; DeWall, Lillehei, and Sellers, 1962; and Gadboys and Litwak, 1963) and that the urinary output in the immediate post-operative period is almost double that obtained when whole-blood primes are used (Zuhdi, Carey, Sheldon, and Greer, 1964). Haemodilution is also said to lessen the danger of sudden unexplained blood volume fluctuations which occur after cardio-pulmonary bypass (Litwak, Gilson, Slonim, McCune, Kiem, and Gadboys, 1961).

Early in our experience with haemodilution perfusions we became concerned with the number of patients who were in a state of undue exhaustion after surgery and with the number who developed severe arrhythmia. As a result we embarked on a prospective study of the biochemical changes during and following bypass.

METHODS

Twenty-six patients were studied (Table I). Using DeBakey pump heads and a disc oxygenator, high flow rates (2·3 l./m.^{2} to 2·5 l./m.^{2}) were maintained even when the mid-oesophageal temperature had dropped to 30° C. (Marchand, Middleton, Benington, and Shreve, 1959; Marchand, Du Plessis, Beckerling, and Durr, 1964). Pure blood was the priming fluid in two cases and diluted blood in twenty-four. In 10 cases the dilution was one part of 5% dextrose water to three parts blood, and in 14 it was two parts of

TABLE I

SUMMARY OF PATHOLOGY, OPERATIVE PROCEDURE, AND HAEMODILUTION USED IN THE 26 PATIENTS STUDIED

Diagnosis	No. of Patients	Operative Procedure
2 : 2 Dilution		
Atrioseptal defect	1	Repair
Rheumatic valvular disease	8	Replacement
Aortic valve disease	1	Valvotomy
Ventricular septal defect	1	Closure
Mitral and tricuspid valve disease	1	Replacement and repair[1]
Pulmonary stenosis	1	Repair
Lutembacher's syndrome	1	Repair
Total	14	
1 : 3 Dilution		
Rheumatic valvular disease	5	Replacement
Atrioseptal defect	1	Closure
Mitral and aortic valve disease	1	Valvuloplasty
Mitral and aortic valve disease	1	Mitral valvotomy Aortic valve replacement
Ostium primum A.S.D.	1	Repair
Obstructive cardiopathy	1	Relief
Total	10	
Pure Blood		
Aortic valve disease	1	Replacement
Atrioseptal defect	1	Closure
Total	2	

[1] Tricuspid valvuloplasty.

5% dextrose water to two parts blood. Heparinized blood, less than 24 hours old, was used. The 2:2 dilution was used for the first 14 patients and the 1:3 dilution for the next ten. Mannitol, 25 g., was added to the priming fluid because of its alleged renal protective properties (Norman *et al.*, 1964). The anaesthetist did not purposely hyperventilate the lungs before but did so mildly after bypass.

Diuretics were stopped seven days before operation, and these patients were given 2 g. potassium bicarbonate daily by mouth for five days. On each of the two pre-operative days patients received 4 g. potassium chloride orally as a liquid, regardless of whether they had been on diuretics or not.

The blood urea, serum sodium, potassium, chloride, and CO_2 content were measured pre-operatively and every six hours post-operatively for six days, starting immediately after completion of surgery. Post-operative assessments of the degree of acidosis were made in 20 patients. Nine of these patients had 1:3 dilutions, nine had 2:2 dilutions, and two had pure blood primes.

The urinary potassium excretion was measured over 24 hours in five patients receiving the 2:2 dilution. The blood urea, serum sodium, potassium, chloride, CO_2 content, and urinary urea were measured in an AutoAnalyzer and the urinary sodium and potassium by flame photometry. The oxygen-carrying capacity of the blood was measured by the method of Peters

TABLE II

No.	Age	Sex	Pre-op. Diuretics	Electrolytes (mEq/l.) Pre-operative Urea	Na	K	Cl	CO_2	Post-operative Urea	Na	K	Cl	CO_2	*p*H as $NaHCO_3$ Required (mEq/m.[2])	Length of Bypass (min.)	Urinary Output (ml./ 1st 24 hr)
2:2 Dilution																
1	15	F		23	136	4·4	99	25	28	144	2·9	93	32·5	120·48	35	1,440
2	50	F	+	36	135	4·1	97	23	74	140	2·4	85	20·4		90	700
3	39	F		31	131	4·8	96	20·5	31	135	2·9	91	27	104·16	30	550
4	35	F	+	35	142	3·4	101	24	45	138	2·4	90	27	235·29	95	1,480
5	53	M		31	136	3·7	104	21·5	28	143	2·6	98	28	338·54	50	625
6	53	F	+	43	135	3·8	98	24·5	73	131	3·3	96	22		91	600
7	16	M		31	139	5·3	98	24	38	141	3·1	94	31·5	138·89	75	2,110
8	27	F		34	126	4·0	92	20	32	131	2.8	80	25·5	296·05	60	950
9	27	M	+	34	136	4·7	100	22	30	141	3·4	93	34·5	307·26	150	1,300
10	16	F		23	139	4·5	104	20	23	127	3·1	92	18	133·33	40	830
11	24	M		55	138	4·4	100	22·5	59	137	2·7	116	22·5		45	700
12	5	F		26	136	4·3	92	28	31	133	2·6	95	28	156·25	18	400
13	4	F		21	140	4·3	95	21	21	138	2·4	87	27			700
14	12	F		26	141	4·8		25	32	135	3·1		26		40	350
1:3 Dilution																
1	58	M		19	134	4·2	89	28	36	138	2·7	91	28		60	800
2	25	F		30	147	4·6	97	14	32	138	2·8	96	24	93·75	39	1,000
3	30	F		30	126	4·9	88	24	38	130	3·8	98	23	156·25		580
4	43	M		34	127	3·7	92	22	43	143	2·7	96	25·5	138·12	50	1,040
5	41	F	+	21	133	4·8	94	29·5	22	147	2·8	97	28	66·67	85	1,000
6	35	F	+	30	141	4·8	104	24·5	28	135	2·6	93	24·5	156·25	122	600
7	28	F	+	16	136	4·5	100	26	46	143	3·0	100	26·5	126·58	60	1,150
8	29	M		34	136	4·5	99	22·5	34	135	3·8	97	25	58·82	35	1,540
9	40	F	+	47	134	3·5	91	31	36	137	3·2	91	31	101·35		1,430
10	35	M	+	31	143	4·3	102	30	30	139	3·9	99	24	166·67	45	700
Pure Blood																
1	34	F		21	136	3·9	93	25	26	127	3·7	96	19		60	900
2	67	M	+	22	134	3·4	85	28	47	138	4·2	91	27		60	750

and Van Slyke (1932) and the arterial blood *p*H and P_{CO_2} and standard bicarbonate by the method of Siggaard Andersen, Engel, Jørgensen, and Astrup (1960). The degree of acidosis is represented as the quantity of sodium bicarbonate (mEq/m.^{2} body surface area) needed to return the *p*H to normal.

RESULTS

The observations of acid base and electrolyte balance are set out in detail in Table II. When changes occurred during the day of surgery, corrective measures were immediately taken, making it impossible to follow the later 'natural' course of events.

ACID BASE BALANCE There was no appreciable fall in the *p*H of the priming fluid irrespective of the degree of dilution, and no difference was found between the *p*H of the diluted and pure blood primes. Post-operatively, metabolic acidosis was encountered and there was a direct relationship between the length of bypass and the degree of acidosis (Figs 1, 2, and 3). The average duration of bypass was similar in the two groups: 71 min. in the 1:3 dilution group and 63 min. in the 2:2 dilution group. A direct relationship between the degree of dilution and the severity of acidosis was also apparent (Fig. 4). The group with 1:3 dilutions showed less acidosis (a mean of 118 mEq $NaHCO_3$/m.^{2} being required to correct the acidosis) than those with 2:2 dilutions (where the mean was 203 mEq $NaHCO_3$/m.^{2}).

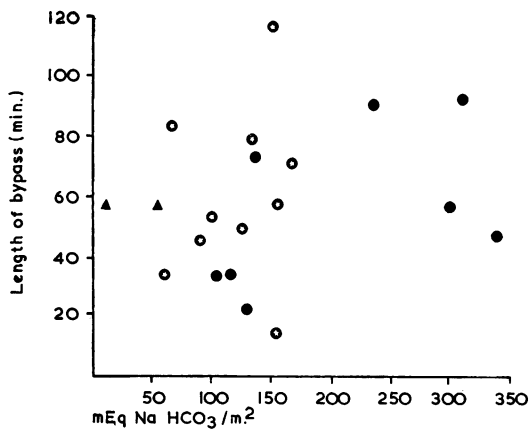

FIG. 1. *Relationship of the length of bypass to the severity of acidosis in all groups. Although the acidosis increases with the length of bypass, it can be seen that the greater the dilution, the more severe the acidosis for comparable periods of bypass. Acidosis is measured in mEq $NaHCO_3$/m.^{2} required to restore arterial blood* p*H to normal.* ● *2 : 2 dilution;* ✪ *1 : 3 dilution;* ▲ *no dilution.*

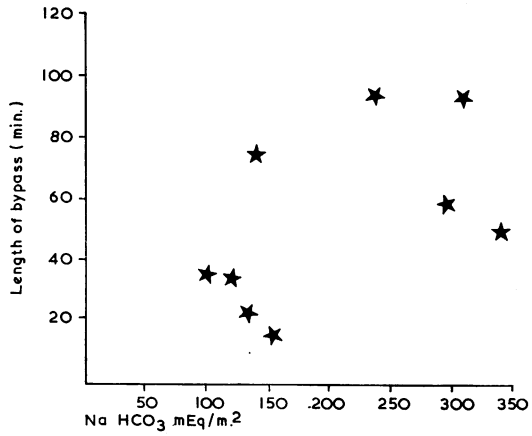

FIG. 2. *Relationship of the length of bypass to the severity of acidosis in the group with 2 : 2 dilution. Increasing length of bypass is associated with increasing severity of acidosis.*

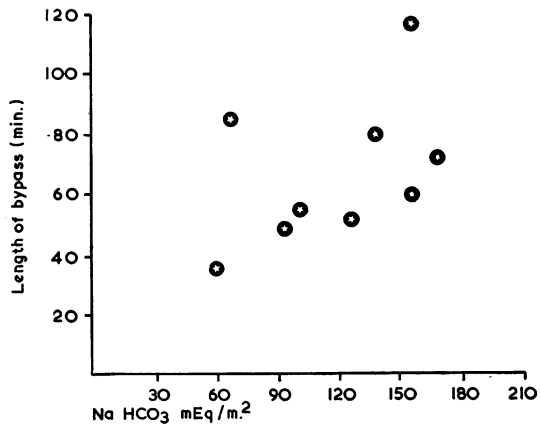

FIG. 3. *Relationship of the length of bypass to the severity of acidosis in the group with 1 : 3 dilution.*

OXYGEN-CARRYING CAPACITY This was only measured in patients with 2:2 dilutions, and the oxygen-carrying capacity was found to be approximately 60% of that of undiluted blood primes.

ELECTROLYTES Major electrolyte changes were found both in the priming fluids and in the circulating blood of the patients during and after bypass. The addition of dextrose water to blood immediately lowered the concentration of all serum electrolytes (Fig. 5; Table III). With the

onset of bypass, when the patient's blood and the priming solution had mixed, the electrolyte concentrations reverted towards normal, and by the end of bypass no major electrolyte disturbance usually remained (Fig. 5). Exceptions were long bypasses of one and a half hours or more. In some of these the serum potassium dropped towards the end of the perfusion, though never lower than 3·3 mEq/litre. Immediately after bypass ended and after the body temperature had been restored the serum electrolytes were normal, with the exception of potassium, which often dropped precipitously during the first hour. The fall in serum potassium concentration occurred in every case where haemodilution was employed, dropping from a mean level of 4·3 mEq/l. preoperatively to a mean of 2·9 mEq/l. postoperatively (Fig. 6). This fall of 1·4 mEq/l. is statistically highly significant ($P<0.01$). The

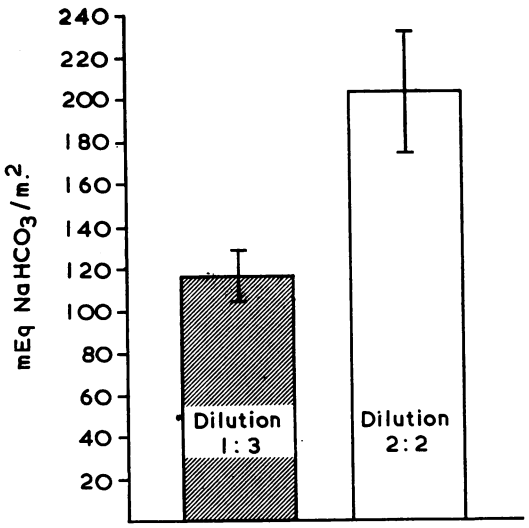

FIG. 4. *Average degree of metabolic acidosis in the two groups each of nine patients with different degrees of haemodilution is compared. This is represented as the quantity of sodium bicarbonate in mEq/m.² body surface area to return the arterial* pH *to normal* (I = *standard error*).

TABLE III

SERUM SODIUM LEVELS (mEq/l.) OF THE PRIME BLOOD BEFORE AND AFTER DILUTION WITH EQUAL PARTS OF 5% DEXTROSE IN WATER

	Serum Sodium (mEq/l.)			
	Before Dilution	After Dilution (D)	Expected Level (E)	Difference (D–E)
	133	100	53·6	46·4
	136	70	37·8	32·2
	139	100	56	44·0
	126	100	50·7	49·3
	130	90	52·4	37·6
Mean	132·8	92·0	50·1	41·9

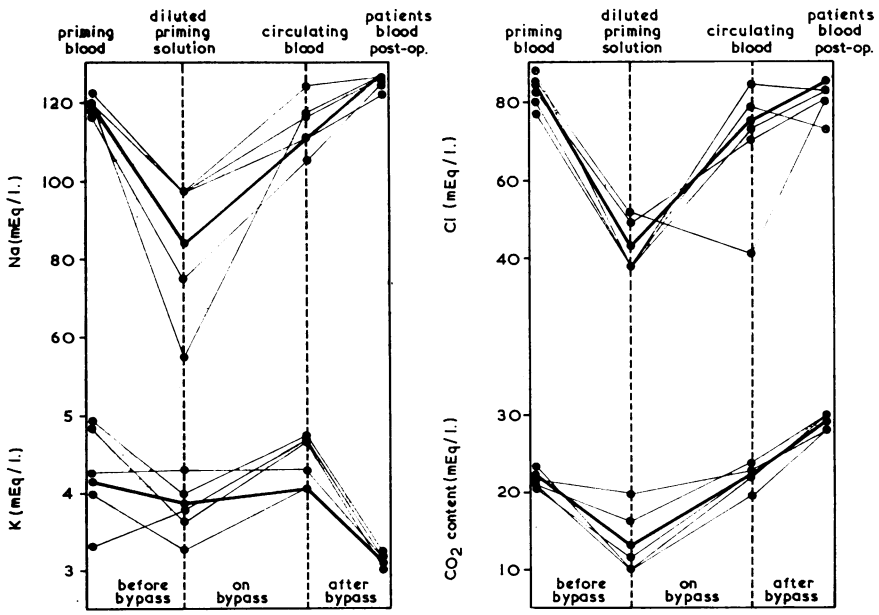

FIG. 5. *Serum electrolyte changes of the priming fluid before and after dilution and of the circulating blood during and after bypass in five patients.*

extent of the post-operative fall was related to the degree of dilution but not necessarily to the length of bypass: it was most pronounced in the group with the 2:2 dilution (Fig. 6); only a slight fall occurred in the patients with pure blood primes (0·04 mEq/l.).

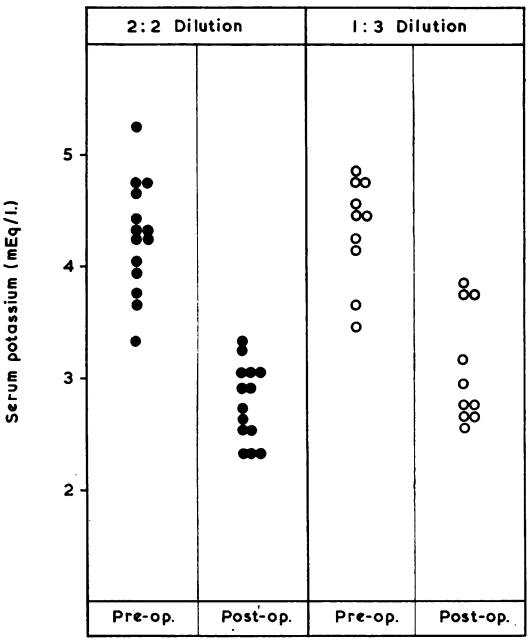

FIG. 6. *Changes in the serum potassium levels before and after operation.*

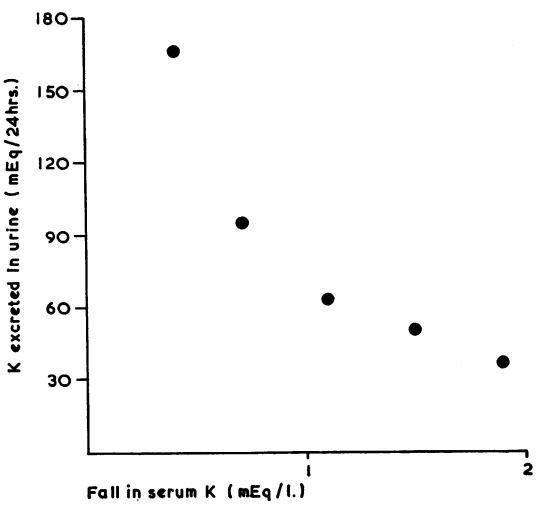

FIG. 7. *Urinary loss of potassium on the day of surgery compared with the fall in mEq from the pre-operative levels.*

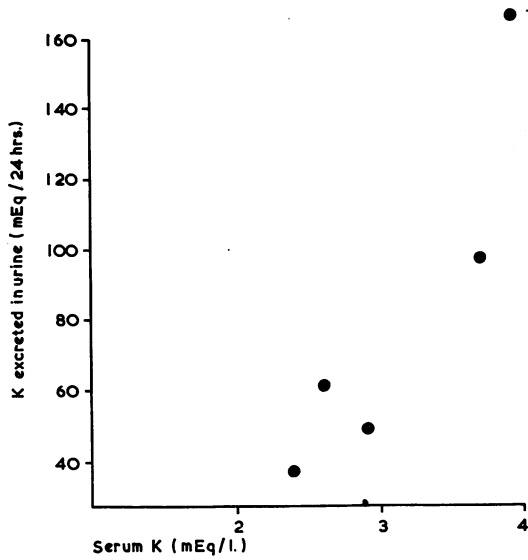

FIG. 8. *Urinary potassium loss compared with the post-operative serum potassium levels in five patients. The high urinary loss of potassium even in the presence of low serum levels is demonstrated.*

Excessive amounts of urinary potassium were excreted during the first 24 hours after surgery. This was measured in five patients and the loss was found to vary from 38 to 164 mEq during the 24 hours (Figs 7 and 8).

DISCUSSION

McCaughan and Lee (1964), Mackenzie, Davies, Masson, and Wade (1963), and Kolff, Effler, and Groves (1960) have all stressed the danger of metabolic acidosis during and after cardio-pulmonary bypass. Metabolic acidosis is probably due to many different causes. The *p*H of the 5% dextrose water supplied to us during the three-month period of this investigation ranged between 4·0 and 4·5. Nevertheless, the *p*H of the diluted priming blood before bypass was normal in all patients; this must have been achieved at the expense of the stored blood buffer. With perfusion the patient's blood buffer is also diluted by the dextrose and water prime (Schlosser and Grotel, 1964) and this dilution may be further enhanced by the entry of water into the extracellular compartment from the cell. Movement of water from the cell is consequent upon the osmotic effect of hyperglycaemia. Under conditions of hypothermia sugar metabolism is impaired, perpetuating the

hyperglycaemia and so increasing the plasma osmolality (Wright and Gann, 1963), an effect which is further enhanced by the use of mannitol.

The effect of dilution of blood buffer is in part to decrease the concentrations, particularly of circulating bicarbonate, whilst CO_2 continues to be produced (Winters, Scaglione, Nahas, and Verosky, 1964). DeWall *et al.* (1962) have mentioned the possibility that the dextrose may result in an excess production of lactate, thus increasing the acidosis. Dilution of haemoglobin favours the production of acidosis ; first, because haemoglobin is an important blood buffer, and, secondly, because dilution of haemoglobin is associated with a decreased oxygen-carrying capacity of the blood. According to Mackenzie *et al.* (1963) the diminished oxygen-carrying capacity may result in hypoxia and consequent acidosis. Arteriovenous oxygen differences during dilution perfusions have been found to be normal, however (Roe, 1963), so this factor is probably not important.

In our experience, acidosis is more pronounced with dilute than with pure blood primes. Acidosis rises progressively with increasing dilution: with the same or even shorter periods on bypass, patients with 2:2 primes suffered more acidosis than those with 1:3 primes (Figs 1 and 4). These observations do not agree with the findings of McCaughan and Lee (1964). Mackenzie and his co-workers (1963) feel that hyperventilation may cause metabolic acidosis by increasing the bicarbonate loss in the urine. However, we never found that an alkaline blood *p*H preceded the onset of acidosis. Moreover, acidosis and hypokalaemia occurred simultaneously, so that the hypokalaemia cannot be attributed to either metabolic or respiratory alkalosis.

The initial dilution of the serum electrolytes of the priming blood was corrected by the end of bypass, usually soon after bypass began. The later CO_2 changes were affected by the therapeutic steps which were taken to combat acidosis, and cannot therefore be accurately interpreted. The fall of serum sodium in the priming fluid was less than would be expected to result from simple dilution (Table III). The expected fall can be calculated from the dilution of plasma sodium by taking into account the haematocrit of the blood before and after dilution. The difference between the expected and the observed levels indicates that sodium had moved from an intracellular to an extracellular phase. Neither clinical nor biochemical hyponatraemia occurred post-operatively. The fact that there is only a slight fall of the serum potassium in the diluted priming blood is also explicable on the basis of movement of potassium from the red cells into the plasma.

The changes of serum potassium had important post-operative clinical effects. Cardiac arrhythmias were common and one patient died suddenly from ventricular fibrillation on the second day when her serum potassium was 2·8 mEq/litre. A second patient, with low serum potassium, developed ventricular fibrillation on return to the ward. She was resuscitated by countershock and there was no recurrence of arrhythmia following the administration of intravenous potassium chloride. In three patients, after valve replacement (two not included in this series), repeated attempts at electrical defibrillation while still on bypass were ineffective until potassium was given. This suggests that the serum potassium was abnormally low, as does the fact that the fibrillating hearts were hypertonic and contracted ; unfortunately, blood samples were not taken. An increased incidence of ventricular fibrillation with haemodilution has been observed by McCaughan and Lee (1964).

All patients with low serum potassium levels developed ventricular extrasystoles which were often multifocal and multiple. The extrasystoles were most severe when the serum potassium level was lowest ; they responded to the administration of potassium and virtually disappeared when the serum potassium was restored to normal. In our opinion, arrhythmia induced by hypokalaemia is the most important complication of haemodilution (Obel, Marchand, and Du Plessis, 1965). Extrasystoles often presage more serious arrhythmias, particularly ectopic ventricular tachyarrhythmias. All the patients in this study had received digitalis. It is therefore possible that hypopotassaemia produced digitalis intoxication with consequent rhythm disturbance, as described by Lown, Wyatt, Crocker, Goodale, and Levine, in 1953, but it is known that hypopotassaemia alone may cause arrhythmia (Young, Sealy, and Harris, 1954).

Early in our experience with haemodilution we noticed that, post-operatively, patients who were unusually listless and atonic responded to the administration of potassium. One patient developed a myasthenia-like state with bilateral external ophthalmoplegia which recovered after potassium administration. Working with dogs, Kahn, Hidalgo, Steude, Ericsson, Lee, and Sloan (1963) observed that the greater the degree of haemodilution the more lethargic was the animal on recovery. Zudhi and co-workers (1964) found

that neurological complications are more common after dextrose-water priming than after pure blood perfusions.

Low levels of serum potassium could result from excessive urinary excretion, from movement of the ion into the cell, or from both. The urinary excretion of potassium during the first post-operative 24 hours has been compared with the fall in serum potassium in five patients, and no positive correlation emerges (Fig. 7). This is expressed in another way in Fig. 8, where the measured post-operative serum potassium is compared with the 24-hour urinary potassium excretion on the day of operation. High potassium excretions occurred even when the serum level was low. In two patients the urinary loss was as high as 160 and 100 mEq/l. in 24 hours. De Wardener (1961) has stated that with a serum potassium of less than 3·0 mEq/l. the excretion of more than 20 mEq of potassium in the urine over 24 hours indicates a renal leak. On this basis a renal leak of potassium is shown in all five patients in whom urinary loss of potassium was measured. These randomly selected patients had previously normal serum potassium levels, and the renal leak must have been acutely acquired and related to bypass. However, this degree of urinary potassium loss over 24 hours cannot account for the total fall in serum potassium. To account for the excessive fall, potassium must also move from an extracellular to an intracellular phase. It has been suggested by DeWall *et al.* (1962) that this accompanies the movement into the cell of glucose derived from the priming fluid. The fall in serum potassium usually corresponds with the restoration of normal body temperature and the resumed normal glucose metabolism. Presumably the potassium content of the renal tubular cell similarly increases and the urinary leak of potassium is due to its high intracellular concentration in the renal tubular cells as described experimentally by Flemma and Young (1964). Barnard, Saunders, Eales, and Barnard (1966) have stated that post-bypass hypokalaemia is probably due to alkalosis; we feel, however, that this is unlikely to be the sole cause but may contribute to or unmask abnormal potassium dynamics.

DeWall *et al.* (1962) and Paton, Rosenkrantz, and Blount (1964) have observed a fall in potassium after haemodilution perfusions. Paton *et al.* consider the fall to be insignificant, whilst DeWall *et al.* have noted a drop from 3·4 to 3·1 mEq/litre. We often leave mixed blood in the machine after bypass, whereas these authors routinely return all the fluid to the patient. This cannot be the only explanation for our different results, because the delayed and marked drop in serum potassium has occurred even when the entire contents of the machine have been returned to the patients.

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