

# PLASMA ELECTROLYTE CHANGES IN HYPOTHERMIA

BY

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Despite the widespread use of hypothermia in clinical surgery, the nature of the plasma electrolyte changes associated with this state is far from clear, and little attempt has been made to consider them in relation to adrenocortical activity.

Haemoconcentration has been recorded in hypothermia by Rosenhain and Penrod (1951), Millar (1954), and Villalobos, Adelson, and Barila (1955), although Segar, Riley, and Barila (1956) and Moyer, Morris, and De Bakey (1957) showed only slight variations in haematocrits which were insignificant but usually indicative of haemoconcentration. This suggests that haemoconcentration is a frequent though not consistent result of hypothermia.

The plasma sodium response to hypothermia is confused. A decrease is reported for hypothermic dogs (Swan, Zeavin, Holmes, and Montgomery, 1953), although Segar *et al.* (1956), also with dogs, found no significant change in the excretion of sodium. In contrast Moyer *et al.* (1957) suggest a rise in plasma sodium for both dogs and man as a common occurrence, although they attach no significance to this change.

Of all the reported changes in blood constituents in hypothermia a fall in the plasma potassium is the most consistent (Swan *et al.*, 1953; Segar *et al.*, 1956; Moyer *et al.*, 1957), although Elliott and Crismon (1947) and Bigelow, Lindsay and Greenwood (1950) had earlier reported a rise. The aetiology of this potassium shift is poorly understood. The diminished plasma potassium does not represent a net loss of body potassium as measured by the urinary loss of potassium during cooling (Swan *et al.*, 1953; Segar *et al.*, 1956; Moyer *et al.*, 1957). Most frequently the movement of potassium from the plasma in hypothermia is attributed to plasma pH changes.

It has recently been shown (Munday and Blane, 1958) that the electrolyte changes of normal intact animals exposed to cold is compatible with the theory of an increased adrenal release of mineralo-corticoid type hormones in response to

the cold stress. Investigations were carried out and are recorded in this paper on the nature of the plasma electrolyte response of the anaesthetized, cold-exposed animal. Such animals become hypothermic compared with the unanaesthetized animal, which maintains its body temperature. There is also controversy as to the adrenal activity and responsiveness in the anaesthetized hypothermic animal, and consequently the investigations on the plasma electrolyte response of the hypothermic animal were extended to consider any possible correlation with adrenal cortical activity.

## MATERIALS AND METHODS

**ANIMALS.**—The rats and rabbits were from departmental animal house stocks. The rats were adult males of the hooded strain and the rabbits adult male litter mates. The clinical samples were collected from patients of both sexes and varying ages suffering from a variety of cardiac disorders demanding surgical treatment. The majority of cases were repairs of atrial septal defects of the ostium secundum type.

**ANAESTHESIA AND HYPOTHERMIA IN RATS AND RABBITS.**—Since curare type drugs cannot be generally used in animal experimentation, the control of the gross shivering necessary for the smooth induction of hypothermia depends entirely on the level of anaesthesia.

Rats were given 5.0 mg. "nembatal"/100 g. body weight intraperitoneally 30 minutes before immersion in the cooling bath and a second dose of 2.0 mg./100 g. a few minutes before immersion. At this dose level the control of shivering was adequate and body temperature fell smoothly.

The rabbits were given 5.0 mg. "nembatal"/100 g. body weight intraperitoneally two hours before immersion and were maintained on a warm bed at 37° C. throughout this period to maintain their body temperature. A second dose of 2.5 mg. "nembatal"/100 g. body weight intraperitoneally was given 30 minutes before immersion. At this dose level all rabbits shivered on immersion in the cooling bath until their body temperature fell to about 25° C. This was unavoidable since administration of higher doses of anaesthetic were frequently fatal.

The anaesthetized rats and rabbits were cooled by immersion in a cooling water-bath. The bath temperature (37° C. at the start) was lowered by the addition of ice, and when the colonic temperature had reached the required minimum (20–24° C.) the bath temperature was raised to that level to prevent a continued fall in body temperature.

For rabbits where serial blood samples were taken from individuals the animals were slowly rewarmed on a heated bed at 37° C.

**ANAESTHESIA AND HYPOTHERMIA IN MAN.**—Induction was by thiopentone after premedication with chlorpromazine and pethidine and sometimes atropine or hyoscine. Shivering was controlled by curare. The patient was surface cooled in an ice-bath to an oesophageal temperature of 32–33° C., and then removed and usually maintained at a temperature of 29.5 to 30.5° C. during cardiomy. After cardiomy the body temperature was restored to normal by surface rewarming with warm water blankets.

**BLOOD SAMPLING.**—For the rats and rabbits all blood samples were taken by cardiac puncture using a paraffined 5 ml. record syringe and a 2 in. (No. V) serum needle. Since blood sampling is itself stressful, rats were rejected after providing one sample, and took no further part in any experiment.

Serial blood samples of approximately 3 to 4 ml. were taken from individual rabbits to parallel the continuous series of the clinical material.

The clinical samples were taken at intervals throughout the operation. Samples were obtained from superficial veins of the arm or leg before and after thoracotomy, care being taken to sample a limb into which there was no saline drip, so avoiding any possible direct dilution effect. While the heart was exposed samples were always taken by direct right atrial puncture.

All blood samples were heparinized, and it was shown that the amount of heparin used introduced no detectable error in the plasma sodium and potassium levels. Any blood sample showing a suggestion of haemolysis after centrifugation was discarded for the plasma potassium value, since correction using spectrophotometric estimation of the degree of haemolysis as suggested by Hunter (1951) proved unsatisfactory. The absence of haemolysis in the clear plasma samples was confirmed by the benzidine test for haemoglobin.

**PROCEDURES.**—Plasma sodium and potassium levels were determined using an "EEL" flame photometer. The plasma was routinely diluted, 1 ml. plasma: 99 ml. glass-distilled water, 1 ml. 5% A.R. HCl. The acid prevented protein precipitation and gave clear solutions and was added in similar proportion to a standard containing  $\frac{145}{100}$  mEq./l. sodium and  $\frac{5}{100}$  mEq./l. potassium. This standard was used in the estimation of both sodium and potassium plasma concentrations and takes account of the radiation interference of large amounts of sodium in determinations of low concentrations of potassium (Lundgren, 1953).

TABLE I  
EFFECT OF HYPOTHERMIA AND TOTAL HEART OCCLUSION IN MAN ON PLASMA SODIUM, POTASSIUM, AND HAEMATOCRIT LEVELS

Patient	Age	Control			In Ice Bath			Pre-occlusion			Post-occlusion			Post-operative			Time After Operation Began (hr.)				
		Na	K	Haema-tocrit	Oesopha-geal Temperature (°C.)	Na	K	Haema-tocrit	Oesopha-geal Temperature (°C.)	Na	K	Haema-tocrit	Time Post-occlusion (min.)	Na	K	Haema-tocrit					
1 J.N.	12	140.1	3.94	35.7	31.5	147.5	4.75	41.3	30.0	150.0	3.39	42.3	30.0	156.3	3.50	41.8	15	150.6	4.40	41.8	6
2 S.H.	14	148.0	5.29	44.1	33.0	148.1	3.83	37.8	30.5	147.5	4.78	42.3	29.3	153.0	2.81	39.1	20	161.8	4.06	43.0	5
3 M.B.	22	148.1	4.09	36.3	33.3	147.5	5.66	41.5	30.25	147.5	4.78	42.3	29.25	148.2	4.27	43.0	36	154.3	3.72	38.0	5
4 L.H.	45	144.2	4.33	42.0	30.8	148.1	3.98	38.0	30.5	151.5	3.84	39.3	31.5	152.2	3.26	41.3	18	153.3	4.04	40.5	8
5 S.C.	14	143.4	4.67	39.2	31.0	148.3	2.60	38.0	31.0	148.3	3.68	38.0	31.0	147.0	4.09	42.0	51	147.0	4.09	42.0	51
6 C.U.	8	145.8	3.94	37.0	35.5	155.5	7.72	80.5	30.2	159.7	5.74	83.0	31.0	154.8	3.68	37.0	41	148.3	3.68	37.0	41
7 J.R.	37	149.0	9.36	82.8	36.0	150.0	4.31	40.0	30.75	150.0	4.08	41.0	31.0	150.0	3.92	43.3	7	154.8	8.11	82.0	41
8 E.C.	28	149.1	4.88	39.5	32.5	160.0	4.88	38.3	30.0	150.1	4.42	43.3	30.0	148.4	3.98	46.9	16	141.6	4.16	41.0	9
9 K.S.	49	146.8	5.14	44.0	34.4	141.6	4.28	54.0	30.8	144.1	4.35	36.0	30.8	153.5	3.84	45.5	6	135.0	3.76	44.0	51
10 F.B.	41	141.8	4.33	36.3	34.4	146.5	3.48	32.5	30.9	148.0	3.04	37.8	30.8	149.1	4.56	40.0	15	148.4	4.75	45.0	10
11 G.W.	28	140.0	4.47	56.0	36.4	146.5	4.0	41.0	30.4	148.0	2.59	35.0	31.0	150.0	2.59	38.0	7	141.7	5.95	49.0	20
12 J.L.	10	146.5	4.0	36.4	32.6	145.0	4.23	41.5	28.3	148.3	3.41	45.5	29.8	143.5	2.44	33.0	14	141.8	4.35	49.0	42
13 W.K.	45	139.0	4.53	41.0	32.6	140.2	3.65	35.0	29.8	140.2	2.82	35.5	31.0	146.5	2.22	30.0	14	141.8	4.35	49.0	42
14 J.L.M.	24	143.5	5.0	40.0	34.0	144.2	3.15	52.3	30.6	144.2	2.78	51.5	31.0	148.1	3.00	39.0	8	141.8	4.35	49.0	42
15 A.P.	10	143.2	3.70	54.8	32.8	144.2	3.15	52.3	30.6	146.8	3.35	39.0	29.5	148.1	3.00	39.0	8	141.8	4.35	49.0	42
16 W.W.	48	145.0	4.16	38.0	33.6	147.9	4.49	44.4	30.35	148.3	3.65	45.0	30.6	149.9	3.34	41.8	8	148.2	4.58	45.8	45.8
Mean		144.6	4.73	44.4	33.6	147.9	4.49	44.4	30.35	148.3	3.65	45.0	30.6	149.9	3.34	41.8		148.2	4.58	45.8	

Plasma electrolyte concentrations in mEq./l. Haematocrit as % cells.

Duplicate whole blood haematocrit determinations were carried out on well-mixed heparinized whole blood samples. All pH determinations were carried out with a Pye "universal" pH meter on whole blood samples taken under oil. The determinations were made at the appropriate temperature within three minutes of the blood sample being withdrawn.

**ADRENALECTOMY.**—The male rats were bilaterally adrenalectomized in one stage under nembutal anaesthesia. They were maintained post-operatively on 1% saline drinking water and rat cake ("blue cross" 41B). On this régime the adrenalectomized animals maintained normal plasma sodium levels, but the plasma potassium levels were somewhat lower than the controls (see Table V). There was a marked haemodilution. The completeness of the adrenalectomy was confirmed in all animals at necropsy.

### RESULTS

**CLINICAL.**—The plasma electrolyte and whole blood haematocrit values were determined from blood samples taken when possible during operations carried out with hypothermia. These patients were in acid-alkali balance. A summary of the series is given in Table I. "Control"

values were obtained immediately before induction of anaesthesia and there was good consistency between these values and those obtained 24 hours earlier before any operative premedication.

Case 3, Table I, is graphically represented in Fig. 1. Comparison with other cases in Table I shows that the trends of change of Case 3 are representative of the series as a whole, and this is further emphasized by Table II in which the changes recorded are expressed as a percentage of the control pre-hypothermia values. These trends are briefly:

(1) A consistent tendency for the plasma sodium level to rise throughout the period of surgery and in most cases to continue rising thereafter. Thus in the first seven cases the highest sodium levels were recorded in post-operative samples taken some three to four hours after the patient had left the theatre, by which time normal or almost normal body temperature had been regained. The sodium levels were normal by the day following the operation.

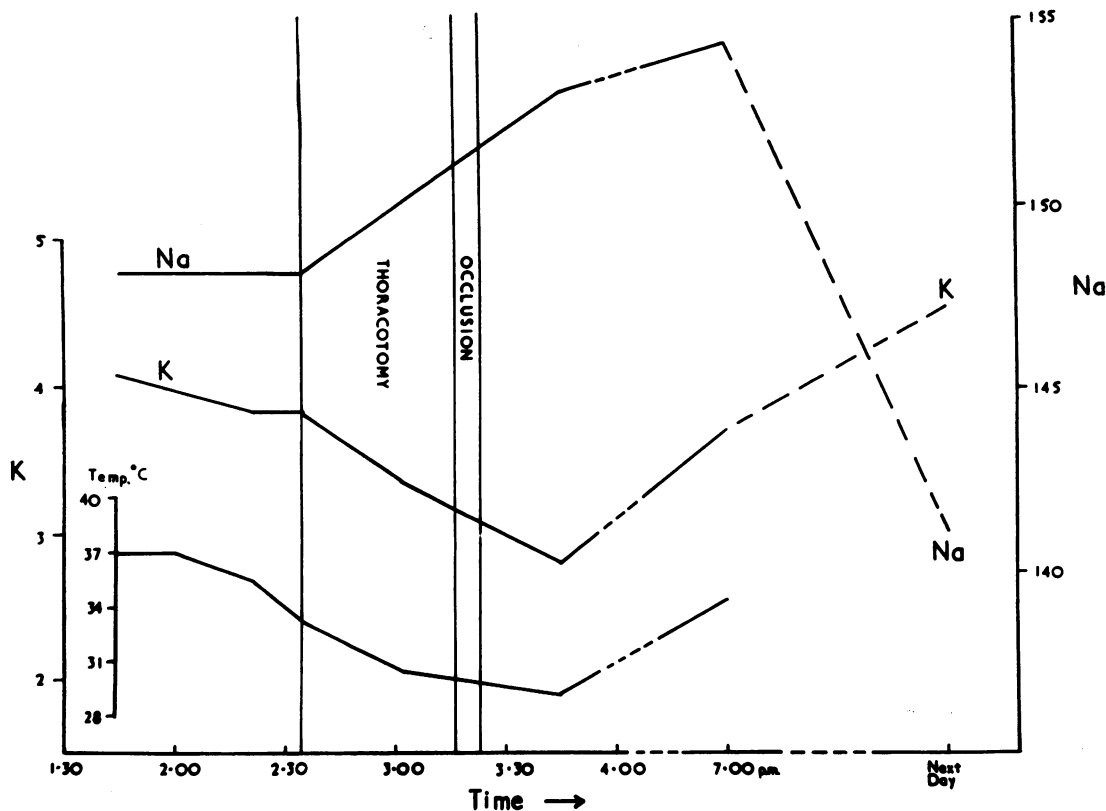


FIG. 1.—Plasma sodium and potassium concentration and oesophageal temperature in clinical hypothermia (Case 3). Electrolyte concentrations as mEq./l. Patient immersed in cooling bath at 2 p.m.

TABLE II  
SUMMARY OF CHANGES IN PLASMA ELECTROLYTES AND WHOLE BLOOD HAEMATOCRITS IN HYPOTHERMIA AT OR NEAR TERMINATION OF SURGERY AS REWARMING BEGAN

Patient	Plasma*		Haematocrit
	Na	K	
2	+5.6	-33.9	-5.2
3	+3.3	-31.4	+7.7
4	+2.8	-1.4	+2.4
5	+6.2	-30.1	+5.4
6	+1.2	-34.0	+2.7
7	+7.2	-38.8	+0.2
8	+0.6	-35.9	+5.8
9	+4.6	-25.3	+3.4
10	+5.1	+5.3	+10.1
11	+5.7	-32.0	+3.2
12	+2.4	-35.2	
13	+6.7	-24.6	+11.0
14		-51.2	-17.5
15	+2.3	-40.1	-8.8
16	+2.1	-27.9	+2.6

\*Results expressed as % individual pre-hypothermia control values.

(2) A very significant fall in the plasma potassium levels, which almost invariably began to fall as soon as cooling commenced before surgery had begun. Minimum levels were recorded towards the end of the operative period, and invariably whenever occlusion took place the post-occlusion level was markedly below the pre-occlusion value. The onset of rewarming after occlusion appeared to check the decline in plasma potassium concentration, and post-operative values, while still slightly low, were often in the vicinity of the control level. The post-operative value was below that of the last surgical sample in only two instances (Cases 4 and 9). There was no evidence of the rise in plasma potassium after thoracotomy described by Mavor, Harder, McEvoy, McCoord, and Mahoney (1956) for dogs.

(3) Whole blood haematocrit changes were inconclusive.

It has been shown that an elevated sodium and depressed potassium concentration in the plasma is a characteristic feature in unanaesthetized rats acutely exposed to cold, and further, that in the absence of the adrenal gland no such changes occur (Munday and Blane, 1958). The close similarity between such an electrolyte response and the pattern observed in patients during and after the induction of hypothermia suggests that here, too, adrenal hyperactivity with release of mineralo-corticoids could be involved. The continued rise in the plasma sodium of most patients, despite the return to normal of the body temperature, tends to contradict any suggestion that the sodium change is a purely physical phenomenon dependent on body temperature itself, and is more compatible with a hypothesis of corticoid release in response to the combined stresses of cooling and major surgical intervention. At the same time these results alone in no way justify the rejection of the conclusion reached by earlier workers that the potassium shift in hypothermia is principally a result of a metabolic alkalosis induced by hyperventilation relative to the reduced needs of the animal. Nevertheless, this should not negate the possibility of mineralo-corticoids acting concurrently and in the same direction as an alkalosis to depress the plasma potassium.

INTACT RATS.—Some questions raised by these clinical results were then investigated by animal experiments. It was first established that the plasma electrolyte and whole blood haematocrit

TABLE III  
PLASMA ELECTROLYTES AND WHOLE BLOOD HAEMATOCRITS OF INTACT RATS BEFORE AND AFTER NEMBUTAL ANAESTHESIA, DURING INDUCTION OF HYPOTHERMIA, HYPOTHERMIA, AND ON REWARMING

Period	Time from Immersion (min.)	Colonic Temperature (°C.)		Plasma Na (mEq./l.)		Plasma K (mEq./l.)		Haematocrit (%)	
			Mean	Level	Mean	Level	Mean	Level	Mean
Control, not anaesthetized	0		38.0		145.6 ±0.21		4.88 ±0.08		42.6 ±0.41
Control, "nembatal" anaesthesia	0	38.2	38.1	145.8	145.7	4.53	4.75	40.0	41.9
		38.2							
		37.8							
		38.2							
Anaesthetized, cooling (0-40 min.)	15	34.0		151.5		4.17		44.5	
	20	33.5		153.5		3.62		47.5	
	25	29.6		155.0		2.92		48.5	
	30	26.0		155.9		3.02		49.0	
Anaesthetized, cold (40-80 min.)	40	22.5		153.0		3.54		52.3	
	55	20.0	23.2	152.5	153.0	3.82	3.81	51.3	
	75	24.0		152.5				51.9	
	80	26.0		153.8		4.06		52.0	
Rewarming 100 min. after removal from bath. Body temperature normal	180	37.5		150.9		4.46		52.0	
	180	38.5	38.0	149.2	150.9	4.34	4.44	55.9	
	180	38.1		152.5		4.51		49.0	
280 min. after removal from bath	360	37.8		148.1		4.61		51.0	
	360	36.6	37.3	148.4	148.5	4.69	4.66	51.5	
	360	37.5		149.0		4.69		51.5	

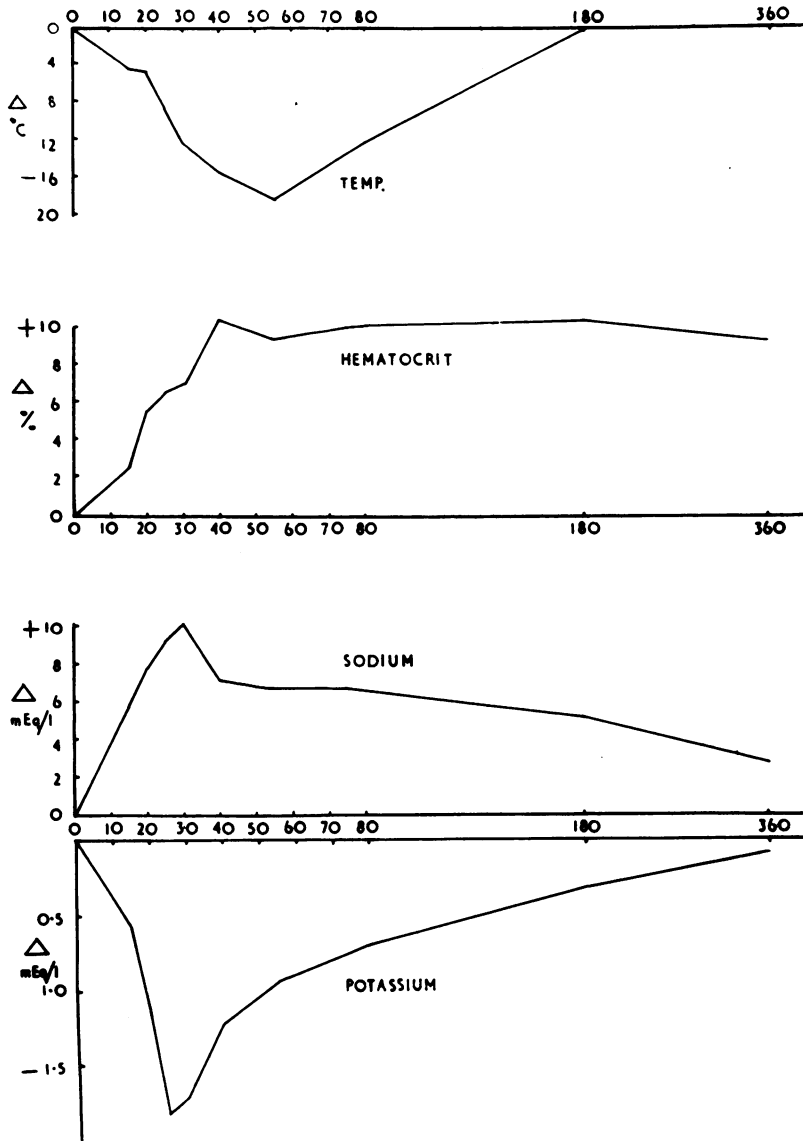


FIG. 2.—Plasma sodium and potassium and whole blood haematocrit changes in intact rats during, and immediately after, hypothermia. Baselines in figure represent control means.  $\Delta$  = Net change from these means.

levels remained normal in "nembutal" anaesthetized rats which were not cooled (Table III).

Other rats were anaesthetized and cooled as described earlier, and blood samples were obtained and analysed at various stages (Table III and Fig. 2).

A consistent record was obtained of rapidly rising plasma sodium and whole blood haematocrit values as hypothermia was induced. At the same time plasma potassium fell to low levels.

The haematocrits remained high throughout the period of deep hypothermia (30–80 min. after immersion in the cooling bath) and were still high when the last rat was sampled 260 minutes after rewarming had begun. By this time the body temperature had been normal for approximately 180 minutes. This clearly defined haemoconcentration of the rat in hypothermia agrees with that recorded by certain earlier workers but contrasts with the haemodilution which occurs in

cold-exposed normothermic rats (Munday and Blane, 1958). It may represent fluid shifts caused specifically by hypothermia, and taking some time to adjust.

Plasma sodium reached a high maximum level within 30 minutes after cooling began and then fell somewhat but remained high until after the animals were rewarmed. In contrast the potassium, while reciprocating the early sodium picture and reaching very low values after 25 to 30 minutes of cooling, climbed steadily throughout the "cold" period. By the end of the six-hour experimental period potassium levels were almost normal.

The hypothermic rats of this experiment received no artificial respiration and were ventilating at a very slow rate. It seemed possible, therefore, that a metabolic acidosis might be present due to inadequate disposal of CO<sub>2</sub>. Sufficient blood for pH determination, as well as electrolyte analysis, could not be obtained from an individual rat and consequently a second group of rats were used to test the blood pH changes in hypothermia. The rats were anaesthetized and half their number (five) cooled as before. The other five were kept at body temperature (37° C.) to act as controls. Blood samples were taken from both sets of animals over a period when electrolyte changes in the hypothermic rats were known to be maximal and the pH determined in each case immediately after withdrawal. The results from control and hypothermic animals are detailed in Table IV, together with the respiratory rates of the animals immediately before sampling.

It is seen that a marked acidosis was present in the hypothermic animals, significant at the 1-0.1% level (t=8.10). While the rate of ventilation was depressed in these rats to one third of the control level it does not necessarily follow that CO<sub>2</sub> retention was the cause of the acidosis, although this is the most probable explanation. The possibility remains that impairment of kidney function at least contributes to the conditions.

This finding of an acidosis in hypothermic rats, concomitant with a low plasma potassium level, renders the more necessary some other interpretation than that previously put forward for this well-established electrolyte change in hypothermia, since an acidosis alone is known to favour the development of hyperkalaemia (Fenn and Asano, 1956; Tobin, 1956). Axelrod and Bass (1956) and Boéré (1957) had also reported low plasma potassium levels in acidosed hypothermic subjects. These results again direct attention to the hypothesis that a sudden release of mineralo-corticoids due to adrenal hyperactivity in response to hypothermia may be responsible for the rapid fall in plasma potassium concentration.

ADRENALECTOMIZED RATS.—To test this hypothesis eight bilaterally adrenalectomized rats were cooled using an identical procedure to that for intact animals. The body temperature of all adrenalectomized animals was found to be slightly subnormal initially (average 36.5° C.). There was little gross shivering during the induction of hypothermia and the rats cooled rapidly to below 25° C. Thereafter they were maintained at body temperatures similar to those reached in the earlier investigation using intact rats (Table III) until the last one had been sampled. Plasma electrolytes and haematocrits were determined for six anaesthetized adrenalectomized controls as well as for the adrenalectomized animals subjected to hypothermia (Table V).

There was no significant change in the level of plasma sodium or potassium on either "nembutal" anaesthesia or hypothermia of the adrenalectomized rats, although there was some haemoconcentration, particularly in hypothermia. Since post-experimental necropsies, performed on all animals participating in this experiment, showed that adrenalectomy had been complete in every case, it is concluded that the sodium and potassium shifts seen in intact rats are, in fact, both dependent on the presence of the adrenal gland, the hormones of the mineralo-corticoid group probably being the responsible agents.

INTACT RABBITS.—A series of small blood samples was taken from individual rabbits. They

TABLE IV  
BLOOD pH AND RESPIRATORY RATE OF NORMAL AND HYPOTHERMIC MALE RATS ANAESTHETIZED WITH NEMBUTAL

Rat	Time from Induction of Anaesthesia (min.)	Colonic Temperature (°C.)	Blood pH	Respiratory Rate/Minute
<i>Normal (Control)</i>				
1	50	37.0	7.50	90
2	50	37.0	7.48	92
3	65	37.6	7.60	92
4	85	37.4	7.60	53
5	90	37.3	7.54	85
Mean	68	37.3	7.54	82
<i>Hypothermic</i>				
6	30	22.5	7.27	24
7	40	23.0	7.05	36
8	50	21.0	7.18	23
9	55	23.0	7.09	Irregular
10	80	22.8	7.20	30
Mean	51	22.5	7.16	28
Δ	-17	-14.8	-0.38	-54

Δ = Change from control means.

TABLE V

PLASMA ELECTROLYTES AND WHOLE BLOOD HAEMATOCRITS OF NORMAL, ADRENALECTOMIZED, ANAESTHETIZED ADRENALECTOMIZED, AND ANAESTHETIZED ADRENALECTOMIZED RATS RENDERED HYPOTHERMIC

	Time from Immersion (min.)	Colonic Temperature (°C.)	Na (mEq./l.)		K (mEq./l.)		Haematocrit (%)	
			Level	Mean	Level	Mean	Level	Mean
Normal, intact, non-anaesthetized rats		38.0		145.6 ±0.21 (30)		4.88 ±0.08 (22)		42.6 ±0.41 (12)
Adrenalectomized, non-anaesthetized rats		36.8 (5)		146.1 ±0.42 (5)		4.48 ±0.16 (5)		30.5 ±0.64 (5)
Nembutal anaesthetized controls (adrenalectomized)		37.0	144.3		4.28		34.5	
		38.0	145.0		4.76		33.0	
		36.5	145.8	145.8	4.84	4.51	33.1	31.7
		36.5	147.6	±0.45	4.35	±0.15	31.0	±0.92
		35.4	145.9		3.96		28.8	
Nembutal anaesthetized hypothermic (adrenalectomized)		35.7	145.9		4.86		29.5	
	20	27.0	146.0		4.40		34.4	
	30	18.5	144.3		4.17		37.3	
	35	22.5	146.8		4.51		38.5	
	40	25.0	143.5	145.4	4.30	4.47	37.9	35.6
	45	22.0	145.9	±0.37	4.05	±0.08	33.5	±0.73
	55	19.0	145.9		4.71		32.5	
	65	23.0	145.6		4.48		35.4	
80	23.0	145.3		4.61		35.0		

Means ± Standard errors. Number of animals in brackets.

were anaesthetized with "nembutal" and a control blood sample obtained at normal body temperature. The animals were then cooled for periods from 75 to 160 minutes and several blood samples taken at intervals during cooling and rewarming.

The changes occurring at the end of cooling as rewarming began are summarized in Table VI, and the general pattern of results confirms that already reported in detail for rats. Again a marked fall in plasma potassium was associated with a respiratory acidosis produced as a result of the anaesthesia.

## DISCUSSION

These results show that a marked fall in plasma potassium and a rise in plasma sodium occurs in

rats, rabbits, and humans anaesthetized and deliberately rendered hypothermic. The percentage fall in plasma potassium is markedly greater than the rise in plasma sodium in all animals. There is also a discrepancy in time between the smaller, more sustained rise in plasma sodium and the faster adjustment of the fall in plasma potassium. There was marked haemoconcentration in the hypothermic rats. The explanation of these electrolyte and fluid changes is somewhat problematical.

As the body temperature falls there is a progressive reduction in renal activity, as measured by the renal blood flow and glomerular filtration rate (Andersen and Nielsen, 1955; Page, 1955; Segar *et al.*, 1956; Moyer *et al.*, 1957). Yet both Segar and Moyer and their co-workers show no concomitant fall in urine output but rather a diuresis.

The haemoconcentration, a characteristic feature in intact hypothermic rats, also developed in adrenalectomized animals, confirming the earlier suggestion that this may be a purely physical phenomenon, specifically resulting from the hypothermia.

No theory has been advanced to account for the plasma sodium shifts, probably because of their variability as recorded by earlier workers. The plasma potassium changes have been correlated with the blood pH changes. In hypothermia most workers artificially ventilate at normal rates, yet the metabolic rate and therefore CO<sub>2</sub> production are depressed. Consequently such animals are frequently relatively hyperventilated and therefore alkalosed. It has been shown in normal animals

TABLE VI

SUMMARY OF CHANGES IN PLASMA ELECTROLYTES OF RABBIT AT THE BEGINNING OF REWARMING AFTER PERIODS OF HYPOTHERMIA

Rabbit	Length of Cooling (min.)	Colonic Temperature (°C.) as Rewarming Began	Plasma*		Respiratory Rate*	Change in Blood pH*
			Na	K		
1	75	21.0	+3.35	-24.6		
2	75	20.5	+3.2	-11.8	-47.5	
3	80	23.5	+4.4	-20.3	-72.5	
4	80	24.3	+3.1	-29.4	-79.0	7.55-7.20
5	80	28.5	+0.8	-28.0	-62.5	7.48-7.38
5 (cont.)	Maintained at body temperature 29°C. for further 80 min.	29.0	+0.8	-40.6	-56.2	7.38 steady

\* Results expressed as % individual pre-hypothermia control value.

that elevated potassium levels occur in acidosis (Fenn and Asano, 1956; and Tobin, 1956) and low potassium levels in respiratory alkalosis (MacKay, 1947). This correlation is emphasized by Segar *et al.* (1956) in attributing the fall in plasma potassium of their hypothermic dogs to hyperventilation resulting in a respiratory alkalosis. Their figures show a close inverse relation between plasma potassium level and pH, potassium levels falling during cooling and rising again on rewarming with reciprocal pH changes. With continued hyperventilation Mavor *et al.* (1956) found the fall in plasma potassium reversed after thoracotomy in 31 out of 45 dogs despite a further fall in temperature. They related this rise in serum potassium to increased hepatic glycogenolysis.

In hypothermic animals not receiving artificial respiration an acidosis frequently develops due to respiratory depression despite the falling metabolic rate. Such a "cold-acidosis" was reported by Axelrod and Bass (1956) in hypothermic dogs and by Boéré (1957) in humans. These acidosed animals did not show the high plasma potassium levels expected, but instead there was a slight fall in potassium paralleling falling pH in the dogs (Axelrod and Bass, 1956) and low plasma levels occurred in the acidosed humans (Boéré, 1957). By contrast Bigelow, Lindsay, Harrison, Gordon, and Greenwood (1950) had found high potassium in the plasma of hypothermic dogs which were presumably extremely acidosed since they were allowed to continue natural ventilation until it ceased.

A respiratory alkalosis known to develop in artificially ventilating hypothermic animals will therefore contribute to any hypokalaemia. However, the results reported in this paper show low plasma potassium levels with a highly significant acidosis in rats. Preliminary observations in the humans and rabbits also indicate no marked alkalosis developing during hypothermia although significant hypokalaemia. Consequently some alternative explanation to pH variation is required to account for these plasma potassium shifts.

Barbitone anaesthetics were employed in all cooling experiments in which low potassium levels have been recorded, and Millar (1954) suggests that barbitone anaesthetized animals, whether cooled or not, may be refractory to stressful stimuli which normally cause release of A.C.T.H. This contention is supported by Masserman's (1937) finding that "nembital" and other barbiturates have a selective inhibitory effect on

hypothalamic nuclei and in consequence a decreased eosinopenic response to trauma in normal cats so anaesthetized. In contrast an increased 17-hydroxycorticosteroid secretion from the adrenal vein of "nembital"-anaesthetized dogs has been recorded in response to such stressors as scalding (Egdahl and Richards, 1956) and exposure to 20% CO<sub>2</sub> (Richards and Stein, 1957). In the experiments recorded in this paper "nembital" anaesthesia alone also failed to affect markedly the plasma potassium level, and it is, therefore, doubtful if the low potassium levels are related to the barbitone anaesthetics.

It has also been suggested that the hypothermic animal is unresponsive to all forms of stress possibly through complete autonomic block (Millar, 1954), and supporting evidence for this is provided by Sayers and Sayers' (1948) report that barbitone anaesthetized rats do not exhibit adrenal ascorbic acid depletion after exposure to +3° C. for one hour. The Sayers suggest that a reduction in cellular activity normally associated with the homeostatic adjustment to cold is responsible for the action of barbiturates in preventing any increase of adrenocortical activity in stress.

Direct evidence that adrenal activity is decreased in hypothermic dogs is provided by Egdahl, Nelson, and Hume (1955). They show a steady fall in the 17-hydroxycorticosteroid level of adrenal venous blood with cooling to 75% below the control level at 21° C. and a rise in corticoid output on rewarming. Continuous infusion of A.C.T.H. did not prevent this fall, indicating a direct suppression of adrenal activity by cold. In contrast to these findings Egdahl and Richards (1956) and Boulouard (1957) reported a marked increase in 17-hydroxycorticosteroid output in unanaesthetized animals exposed to severe cold.

While these limited results on the activity of the adrenal cortex in hypothermic anaesthetized animals suggest that corticoid output is depressed in the hypothermic subject, this level may not necessarily be low relative to tissue requirements, which will also be depressed. A state of relative hypercorticoidism might still therefore exist, and, further, Richards and Stein (1957) have shown that changes in the CO<sub>2</sub> content of the blood can stimulate 17-hydroxycorticosteroid release through the ALP. Consequently hyper- or hypo-ventilating animals might themselves cause increased cortical activity.

More recent work on aldosterone suggests its likely implication in the aetiology of the electro-



lyte shifts in hypothermia. Aldosterone is known to be released in response to body fluid electrolyte imbalances (Leutscher and Axelrad, 1954; Rosenfeld, Rosenberg, Ungar, and Dorfman, 1956) rather than A.C.T.H. secretion (Farrell, Banks, and Koletsky, 1956; Rauschkolb, Farrell, and Koletsky, 1956). It is therefore quite possible that aldosterone may be released in the hypothermic animal in response to increased demand from either the fluid shifts that seem to occur in hypothermia or from electrolyte irregularities.

The pattern of the plasma electrolyte response reported in this paper for the intact hypothermic animal is compatible with the hypothesis of a sudden release of mineralo-corticoid type hormones due to adrenal hyperactivity resulting from hypothermia. It is also established that the hypokalaemia developed during hypothermia in the rats is not due to the development of an alkalosis. This theory of adrenal participation is further substantiated by the failure of adrenalectomized hypothermic rats to give the plasma electrolyte response typical of intact hypothermic animals.

Churchill-Davidson (1954) has remarked on the absence of evidence that patients rendered hypothermic suffer less from the reactions of stress than during other forms of anaesthesia, and he has added that the induction of cooling itself may be another form of trauma.

The suggestion in this paper of a possibly adrenally controlled change in the electrolyte pattern of the hypothermic mammal could therefore imply that the pituitary-adrenal axis of anaesthetized animals may not be as refractory to stressful stimuli as many earlier workers have supposed.

#### SUMMARY

In hypothermic rats, rabbits, and humans there is a small sustained rise in plasma sodium levels and a marked fall in plasma potassium levels.

Haemoconcentration occurs in hypothermic rats. This electrolyte response does not occur in hypothermic adrenalectomized rats, although there is some haemoconcentration.

It is suggested that the plasma electrolyte response of hypothermia may be attributable to adrenal cortical hyperactivity, presumably through hormones of the mineralo-corticoid type.

The marked hypokalaemia of hypothermia is not due to the development of a respiratory alkalosis.

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