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A COMPARISON OF CERTAIN ACID–BASE CHARACTERISTICS OF ARTERIAL BLOOD, JUGULAR VENOUS BLOOD AND CEREBROSPINAL FLUID IN MAN, AND THE EFFECT ON THEM OF SOME ACUTE AND CHRONIC ACID–BASE DISTURBANCES

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The exact relationships of carbon dioxide tension (pCO_2) and hydrogen-ion activity (pH) to the chemical control of respiration are still not clearly understood. Attempts to correlate ventilation quantitatively with the pH or pCO_2 of blood under all circumstances have not been successful. One reason for this failure is that arterial blood may not always accurately reflect the changes of pH and pCO_2 within or around the respiratory centre. For example, Lambertsen, Kough, Cooper, Emmel, Loeschcke & Schmidt (1953) found that when normal subjects breathed oxygen at a pressure of 3 atmospheres there was an increase in ventilation and a fall in arterial pCO_2. However, the pCO_2 of the jugular venous blood rose and it was postulated that the increase in ventilation was due to a 'central rise' in pCO_2.

A disparity between pH changes in arterial blood and those occurring within the brain would be expected to occur in metabolic acidaemia and alkalaemia. The blood–c.s.f. barrier is relatively impermeable to bicarbonate, though like other tissues it is freely permeable to CO_2 (Robin, Whaley, Crump, Bickelmann & Travis, 1958; Mitchell, Massion, Carman & Severinghaus, 1960). The c.s.f. and interstitial fluid of the brain behave very similarly with regard to the exchange of ions between them and plasma (Davson, 1956*a*). If the similarity includes the behaviour of the bicarbonate ion the acid–base changes in the c.s.f. should be a guide to those occurring in the brain, and experimental evidence suggesting that this is correct has been given by Stabenau, Warren & Rall (1959).

The present work is concerned with some of the acid–base relationships of arterial and internal jugular blood and c.s.f. in man. Sodium bicarbonate has been used to induce short- and moderately long-term alkalaemia, and the effects of chronic acidosis on the acid–base relationship of

arterial plasma to c.s.f. has been investigated in patients with renal failure. A preliminary report on these findings has already been published (Bradley & Semple, 1959).

METHODS

Sampling of blood and c.s.f. Arterial punctures were made with a Cournand-type needle connected with suitable taps to a length of plastic tubing. In this way samples could be taken without the subject's knowledge. A similar procedure was employed for puncture of the jugular bulb, except that an ordinary hypodermic needle was used. The lumbar-puncture needle was connected to a three-way tap through which the dead space of the tap and syringe could be flushed with c.s.f. before the sample was taken. Samples of blood and c.s.f. (10 ml.) were withdrawn slowly and simultaneously over a period of 3–5 min. With blood dilute heparin-saline was used as an anticoagulant.

When both cisternal and lumbar c.s.f. were sampled the patient was in a sitting position. The patients were anaesthetized with thiopentone and paralysed with succinyl choline chloride. A cuffed endotracheal tube was inserted and the patient was artificially ventilated with oxygen until spontaneous respiration returned. Samples were not taken until the patient had been breathing spontaneously for at least 15 min. No volatile agents were used and the patients breathed oxygen throughout the experimental procedure. The lumbar and cisternal punctures were done simultaneously but cisternal fluid was withdrawn first.

Pulmonary ventilation was measured in the mornings in five basal subjects who were receiving $NaHCO_3$ daily for 5–7 days. The subject breathed air through the mouthpiece, valve and tubing for 15 min., for the last 5 of which expired air was collected in a Douglas bag. The volume was expressed as at body temperature and pressure and saturated with water vapour.

Analysis. Samples were stored in iced water and measurements made within 4 hr. CO_2 content and O_2 content and capacity were measured on 1 ml. samples by the Van Slyke–Neill manometric method (Peters & Van Slyke, 1932); duplicates for CO_2 were required to agree to within 0·1 m-equiv/l. and for O_2 to within 0·1 vol. %. Blood and c.s.f. pH were measured anaerobically at 37·5° C with a capillary glass electrode, a calomel reference electrode in saturated KCl and a vibrating plate electrometer (Vibron 33B electrometer with 33B pH measuring accessory unit; Electronic Instruments Ltd., Richmond, Surrey). The standard reference buffer was 0·025 M-KH_2PO_4 with 0·025 M-Na_2HPO_4 to which was assigned an arbitrary pH value of 6·840 at 37·5° C. The linearity and sensitivity of the response of the electrode system was tested with 0·05 M-C_6H_4(COOH) COOK and 0·05 M-$Na_2B_4O_7$. No significant difference was found in the measured pH of buffers made up in this laboratory and those prepared from chemicals supplied from the National Bureau of Standards, Washington, D.C. In a series of 67 duplicate estimations on blood there was a mean difference in pH of 0·001, S.D. $\pm$ 0·004; for thirty-nine duplicate measurements on c.s.f. the mean difference was 0·002, S.D. $\pm$ 0·005. The small effect of the presence of cells on the estimation of plasma pH has been allowed for by adding 0·01 to the measured pH of the blood (Severinghaus, Stupfel & Bradley, 1956*a*).

Calculations. The pK_1' and solubility coefficient for CO_2 in blood, and their variation with temperature and pH were obtained from the data of Severinghaus, Stupfel & Bradley (1956*a*, *b*). For c.s.f. the solubility coefficient and pK_1' suggested by Alexander, Gelfand & Lambertsen (1960) were used.

The dissolved CO_2 was calculated from the total CO_2 content and pH values; the [HCO_3^-] was obtained by subtracting the dissolved from the total CO_2 content.

RESULTS

The normal acid–base relationships between arterial blood, c.s.f. and jugular venous blood. Table 1 shows the mean values for pH, pCO_2 and $[HCO_3^-]$ of arterial plasma and lumbar c.s.f. in twenty-three normal subjects, together with S.D. of individual observations and the S.E. of the means. In all subjects the c.s.f. pH and $[HCO_3^-]$ were lower than those of the arterial plasma. The pCO_2 of the c.s.f. was always higher than that of the arterial blood and the mean difference was 9·4 mm Hg. In six subjects there was no significant difference between the mean pCO_2 of jugular venous blood and that of lumbar c.s.f. (Table 2). There was some scatter but with the exception of subject 3 the individual differences were small.

Table 3 shows that lumbar c.s.f. did not differ significantly from cisternal fluid in four subjects. Two of them were given 7 g of $NaHCO_3$ intravenously about 2 hr before the samples were taken. This was to see whether secretion from the choroid plexuses or diffusion from brain to c.s.f. was sufficiently rapid to produce a disparity between cisternal and lumbar $[HCO_3^-]$. Plasma $[HCO_3^-]$ increased as expected, but the results in Table 3 show that no disparity was evident 2 hr after the administration of $NaHCO_2$.

Chronic acidosis in patients with renal excretory failure. This was studied in five patients who were in a steady state except for E.M., who had suffered a recent exacerbation. The pH, pCO_2 and $[HCO_3^-]$ of arterial plasma and c.s.f. may be compared with the values from normal subjects in Table 1. In three patients the pH of the arterial plasma was more than 2 S.D. below the mean found in normal subjects. In the other two it was within normal limits, but in one of them the arterial $[HCO_3^-]$ was below the normal range. Although none of the individual values of c.s.f. pH were outside the normal range, all were slightly on the alkaline side of the mean for the normal subjects. This was because $[HCO_3^-]$ in the c.s.f. was much nearer the normal than was plasma $[HCO_3^-]$, while the depression of pCO_2 from the normal was always slightly greater in c.s.f. than in arterial blood. In two patients c.s.f. pH was actually higher than arterial pH, a reversal of the normal finding.

Acute alkalaemia was induced in five subjects by intravenous $NaHCO_3$ (4–9·2 g) given over a period of 10–15 min. Samples of blood and lumbar c.s.f. were taken before and 30–40 min. after the completion of the intravenous infusion, the needles remaining *in situ* throughout the experiment. The absolute values of pH, pCO_2 and $[HCO_3^-]$ are shown in Table 4 and the changes are presented graphically in Fig. 1 (closed circles). These changes are similar to those in dogs (Robin *et al.* 1958). In all subjects

TABLE 1. Acid–base relationships between arterial plasma and lumbar c.s.f. in twenty-three normal subjects and five patients with chronic renal failure

	pH			pCO_2 (mm Hg)			$[HCO_3^-]$ (m-equiv/l.)		
	Plasma	c.s.f.	c.s.f.–plasma	Plasma	c.s.f.	c.s.f.–plasma	Plasma	c.s.f.	c.s.f.–plasma
				Normal subjects					
Mean	7·397	7·307	−0·090	41·1	50·5	+9·4	25·3	23·3	−2·0
S.D.	±0·022	±0·027	±0·026	±3·6	±4·9	±3·7	±1·8	±1·4	±1·2
S.E.	±0·005	±0·006	±0·006	±0·8	±1·0	±0·9	±0·4	±0·3	±0·3
				Renal failure					
E.M.	7·162	7·331	+0·169	25·1	29·8	+4·7	8·8	14·8	+6·0
T.H.	7·251	7·315	+0·064	32·8	37·9	+5·1	14·2	18·0	+3·8
A.S.	7·346	7·322	−0·024	38·4	43·2	+4·8	20·9	20·8	−0·1
P.M.	7·358	7·318	−0·040	31·8	39·6	+7·8	17·8	18·9	+1·1
R.S.	7·371	7·321	−0·050	39·9	47·6	+7·7	23·1	23·0	−0·1

TABLE 2. Simultaneous comparison of pCO_2 (mm Hg) in jugular venous blood and lumbar c.s.f.

Subject	Jugular venous blood	c.s.f.
1	56·7	56·5
2	50·2	51·2
3	48·9	53·8
4	51·1	50·4
5	49·5	47·9
6	40·3	37·9
Mean	49·5	49·6

TABLE 3. Comparison of cisternal and lumbar c.s.f. in four anaesthetized subjects

	pH			pCO_2 (mm Hg)			$[HCO_3^-]$ (m-equiv/l.)		
	Cisternal	Lumbar	Lumbar–cisternal	Cisternal	Lumbar	Lumbar–cisternal	Cisternal	Lumbar	Lumbar–cisternal
1*	7·254	7·274	+0·020	52·0	51·1	−0·9	23·5	24·3	+0·8
2	7·277	7·274	−0·003	46·7	47·4	+0·7	22·2	22·4	+0·2
3	7·254	7·247	−0·007	56·2	55·2	−1·0	25·4	24·5	−0·9
4*	7·318	7·319	+0·001	44·8	44·6	−0·2	23·6	23·5	−0·1
Mean	7·276	7·279	+0·003	49·9	49·6	−0·3	23·7	23·7	0

* 7 g $NaHCO_3$ given intravenously 2 hr before samples taken; in these subjects arterial plasma $[HCO_3^-]$ increased by 3·0 and 3·1 m-equiv/l. over the 2-hr period ending with the sampling of c.s.f.

TABLE 4. Arterial plasma and c.s.f. pH, pCO_2 and $[HCO_3^-]$ before and after $NaHCO_3$ administration

			pH				pCO_2 (mm Hg)				$[HCO_3^-]$ (m-equiv l.)			
			Plasma		c.s.f.		Plasma		c.s.f.		Plasma		c.s.f.	
Subject	Days on $NaHCO_3$	Dose (g/day)	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
(*a*) Acute alkalosis. Normal subjects, before and 40 min after a single intravenous dose of $NaHCO_3$.														
1	—	4	7·443	7·461	7·335	7·314	39·8	39·1	46·9	49·0	27·3	28·1	23·2	23·1
2	—	5	7·402	7·426	7·290	7·260	43·3	43·6	52·3	57·8	26·8	28·7	23·1	23·7
3	—	6	7·397	7·426	7·310	7·291	32·4	34·1	40·4	43·2	20·0	22·6	18·9	19·3
4	—	8	7·383	7·433	7·337	7·323	40·1	41·2	44·8	45·2	23·9	27·8	22·5	22·4
5	—	9·2	7·389	7·477	7·293	7·307	42·3	39·3	52·0	51·3	25·5	29·3	23·3	23·9
(*b*) Chronic alkalosis. Normal subjects before and after receiving daily oral $NaHCO_3$. Subject B.D. received 5 of the 40 g intravenously for the first 3 days.														
E.A.	7	40	7·383	7·402	7·301	7·284	42·3	44·7	53·8	55·7	25·2	27·8	24·6	24·4
R.C.	5	40	7·403	7·439	7·310	7·312	42·3	42·2	52·4	53·5	26·4	28·8	24·5	25·2
D.H.	6	40	7·388	7·452	7·306	7·298	47·2	47·2	53·1	54·9	28·5	33·3	22·9	24·9
B.D.	7	40	7·428	7·410	7·315	7·300	37·7	42·7	50·6	51·9	25·1	27·1	22·7	23·7
R.L.-R.	6	40	7·461	7·431	7·349	7·324	31·7	42·1	43·1	49·3	22·8	28·1	22·2	23·9
H.J.	5	100	7·391	7·473	7·282	7·297	42·4	49·1	56·1	63·7	25·8	36·2	24·5	28·9
(*c*) Patients with chronic acidosis (renal failure), before and after receiving daily oral $NaHCO_3$. Patient P.M. received 6 of the 40 g intravenously for the first 3 days.														
E.M.	5	40	7·162	7·316	7·331	7·313	25·1	36·4	29·8	45·0	8·8	18·5	14·8	21·3
T.H.	7	40	7·251	7·337	7·315	7·306	32·8	32·6	37·9	41·6	14·2	17·4	18·0	19·3
A.S.	6	40	7·346	7·445	7·322	7·319	38·4	50·3	43·2	55·8	20·9	34·8	20·8	26·7
P.M.	6	40	7·358	7·409	7·318	7·311	31·8	44·0	39·6	47·5	17·8	27·9	18·9	22·3
R.S.	7	40	7·371	7·457	7·321	7·306	39·9	46·6	47·6	55·3	23·1	33·0	23·0	25·6

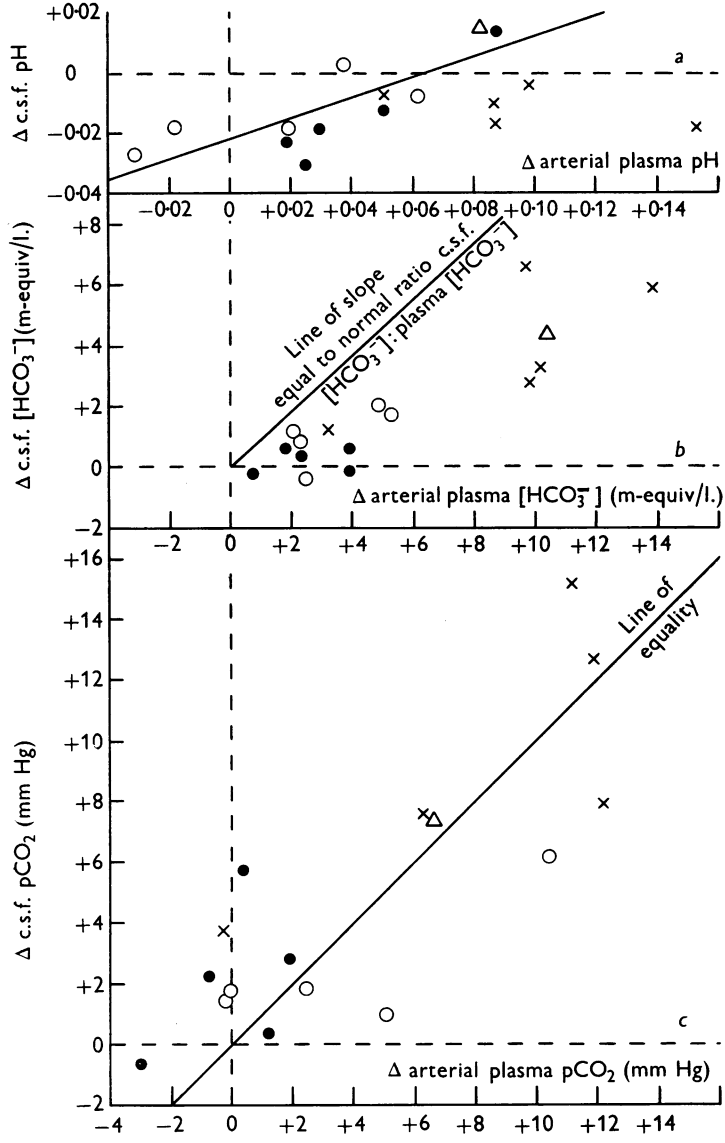

Fig. 1. Changes in plasma and c.s.f. pH, pCO_2 and $[HCO_3^-]$ after $NaHCO_3$ administration. ●, changes occurring 30–40 min after intravenous $NaHCO_3$ in five normal subjects. ○, changes following 5–7 days $NaHCO_3$ by mouth (40 g/day) in five normal subjects. △, changes in one normal subject receiving 100 g/day $NaHCO_3$ for 5 days. ×, five patients with renal failure who received $NaHCO_3$ by mouth, 40 g/day for 5–7 days. (*a*) pH changes. The regression line has been calculated for the normal subjects only and includes the acute and longer-term alkalaemia. (*b*) $[HCO_3^-]$ changes. The line represents the changes in c.s.f. and plasma $[HCO_3^-]$ which would have occurred if the normal ratio c.s.f. $[HCO_3^-]$: plasma $[HCO_3^-]$ had been restored after $NaHCO_3$ (see text). (*c*) pCO_2 changes.

there was a rise in arterial [HCO_3^-] which was roughly proportional to the dose given. The rise in c.s.f. [HCO_3^-] was much smaller or even completely absent. Plasma pH rose whilst c.s.f. pH fell in four of the five subjects. In the fifth the pH of the c.s.f. rose owing rather to an absence of the rise in pCO_2 which occurred in the other four subjects, than to a greater penetration into the c.s.f. of [HCO_3^-]. In the acute experiments, taken in isolation, there was little correlation between the pCO_2 changes in the c.s.f. and in the plasma (Fig. 1*c*).

In two subjects who were not given $NaHCO_3$ no significant change in pH was noted over a 30 min interval, but c.s.f. [HCO_3^-] fell by 0·2 and 0·7 m-equiv/l., which was within the range of experimental error.

Effects of long-term alkalosis in normal subjects. The fall in c.s.f. pH and small rise in [HCO_3^-] in acute alkalaemia observed by Robin *et al.* (1958) and in our subjects may be a feature of short-term experiments only. For about a week five subjects were given $NaHCO_3$ (40 g/day) orally, except that one of them received part of his daily dose (6 g) intravenously on the first 3 days; a sixth subject was given $NaHCO_3$ (100 g/day) by intragastric drip for 5 days. Samples of arterial blood and c.s.f. were taken before and at the end of the period of $NaHCO_3$ administration. Table 4 shows the absolute values for pH, pCO_2 and [HCO_3^-], and the changes observed are recorded graphically in Fig. 1 (open circles and triangle). The changes induced in the normal subjects were often small but the same general trends were observed as with the short-term experiments. The rise in [HCO_3^-] in c.s.f. was again smaller than in the arterial blood. A line having a slope equal to the ratio of c.s.f. [HCO_3^-] to plasma [HCO_3^-] has been derived from the mean normal values in Table 1 (no correction has been made for the different solid contents of plasma and c.s.f.). This line, of slope 0·921, shows the changes in c.s.f. [HCO_3^-] which would have occurred if the ratio had been restored after $NaHCO_3$ administration. In the acute and longer-term alkalaemia the failure to reach this ratio is of approximately the same degree in both groups.

The pH of the c.s.f. fell in four subjects, remained unchanged in one and rose slightly in the subject receiving 100 g of $NaHCO_3$ daily (Fig. 1*a*). In the acute and longer-term experiments in the normal subjects there was a tendency for Δ pH in the c.s.f. to become more positive as the increases in plasma pH became greater. The regression line in Fig. 1*a* has been calculated from the values obtained in these normal subjects and has a significant correlation coefficient of 0·763 ($P < 0·01$). Plasma pH rose in four subjects but fell in two in spite of a rise in plasma [HCO_3^-].

C.s.f. pCO_2 rose in all subjects, but for this group of experiments taken by themselves the correlation between changes in pCO_2 in arterial plasma and in c.s.f. was not striking.

Correction of acidaemia in the patients with renal failure. As with the normal subjects, $NaHCO_3$ (40 g/day) was given for about a week to five patients with renal failure. One of the patients received 5 g of the 40 g intravenously for the first 3 days. The absolute values are shown in Table 4 and the changes in Fig. 1 (crosses). In the patients it was possible to induce larger, more convincing and consistent changes, all of them statistically significant. As in the normal subjects the increase of c.s.f. $[HCO_3^-]$ was about 40 % of that in the arterial plasma and the normal ratio was not reached. In all patients pH rose in the plasma and fell in the c.s.f., though the pH changes in the c.s.f. were small. The relation between Δ pH in the c.s.f. and in plasma appeared to be different from that found in the normal subjects (Fig. 1*a*) and the points have not been used in the calculation of the regression line shown in the figure.

Pulmonary ventilation was measured daily for 3 days in five subjects before and during administration of $NaHCO_3$. Three of the subjects were patients with renal failure, one being severely acidaemic (T.H). The mean of the ventilations recorded on the 2 days before the start of $NaHCO_3$ was compared with the mean for the last 2 days of $NaHCO_3$ administration. No significant change occurred in the two normal subjects. In the three patients the resting ventilations were 10·2 l./min (patient T.H.), 8·0 l./min (A.S.) and 8·1 l./min (R.S.); during $NaHCO_3$ administration, the ventilations were 1·6, 2·2, and 1·6 l./min lower.

DISCUSSION

Acid–base relationships between lumbar, cisternal and ventricular c.s.f.

In our experiments there was no significant difference between lumbar and cisternal c.s.f. even when there had been a stepwise change in plasma $[HCO_3^-]$ 2 hr earlier (Table 3). Cisternal fluid was withdrawn first, and Kroiss (1928) has suggested that the first fluid aspirated from the cisterna magna is predominantly ventricular. If this is correct, there is little difference in pH, pCO_2 and $[HCO_3^-]$ between ventricular and lumbar c.s.f.

Changes in arterial and c.s.f. pCO_2 after $NaHCO_3$ administration

Figure 1*c* shows, that after acute and long-term administration of $NaHCO_3$, changes in plasma pCO_2 were not always matched by equivalent changes in c.s.f. pCO_2, which is illustrated by the scatter of the points around the line of equality. Two possible explanations for this are, first, error in estimating pCO_2, and secondly, changes in ventilation while the samples of blood and c.s.f. were being taken. Any small change in ventilation would quickly and profoundly affect arterial pCO_2, but fluctuations in c.s.f. pCO_2 are probably much smaller because the CO_2 stores of the

tissues and c.s.f. are large relative to those of the blood, and because alterations in cerebral blood flow would be expected to accompany changes in arterial pCO_2 and would tend to maintain venous and hence c.s.f. pCO_2 constant.

The c.s.f. pCO_2 always rose after $NaHCO_3$ administration except in one normal subject. There are three possible causes for this increase, (1) rise in metabolic rate, (2) fall in cerebral blood flow and (3) fall in alveolar ventilation. All experiments were done with the subjects in the basal state, except for two patients who were severely ill, and hence it is unlikely that changes in metabolic rate were primarily responsible for the rise of c.s.f. pCO_2. Apart from one subject, arterial pCO_2 rose or did not alter significantly, and therefore cerebral blood flow would probably have risen or remained constant. It seems probable therefore that the rise in c.s.f. pCO_2 was primarily due to a fall in alveolar ventilation following $NaHCO_3$ administration.

Arterial and c.s.f. pH

In the various acid–base disturbances investigated, including severe acidaemia, c.s.f. pH remained within the range found for our normal subjects (Table 1). Administration of $NaHCO_3$ to the normal subjects and patients gave rise to a wide range of changes of plasma pH. C.s.f. pH usually fell and the changes were much smaller. The smaller fluctuations in c.s.f. pH are related to the changes in the other two variables: changes in the c.s.f. $[HCO_3^-]$ were smaller than those in the plasma and were in the same direction as the changes in c.s.f. pCO_2.

$[HCO_3^-]$ *in c.s.f. and plasma*

C.s.f. $[HCO_3^-]$ was lower than arterial plasma $[HCO_3^-]$ except in severe acidosis. For our normal subjects (Table 1), the mean $[HCO_3^-]$ in c.s.f. and arterial plasma, expressed in m-equiv/kg H_2O, were 23·5 and 27·5, respectively, the ratio being 0·855. This is close to that found in the goat and monkey, but appreciably greater than in other species (Davson & Luck, 1956). The ratio was different in chronic metabolic acidosis, acute alkalaemia and a longer-term alkalaemia of about a week (Fig. 1*b*). We have no evidence that it is ever restored in chronic metabolic acidosis. However, the normal ratio was found in two patients with chronic respiratory acidosis (emphysema with a persistently high plasma $[HCO_3^-]$); in them the c.s.f.: plasma ratios for $[HCO_3^-]$ were 0·86 and 0·85 (unpublished observation).

According to Davson (1956*b*) results obtained by various methods indicate that new c.s.f. is formed at a rate of about 0·3 % of the total volume per minute; whatever assumptions are made about mixing, it seems

unlikely that the total renewal time greatly exceeds 24 hr. It appears from our results that the establishment of a new steady state for the arterial plasma–c.s.f. [HCO_3^-] relation may take much longer than the renewal time for c.s.f.

The chemical control of ventilation

Changes in blood pH induced by adding CO_2 to the inspired air have a greater effect on ventilation than equivalent pH changes produced by non-gaseous means, such as administration of $NaHCO_3$ and NH_4Cl without control of pCO_2. The difference could be accounted for by the impermeability of the blood–c.s.f., and probably the blood–brain, barrier to bicarbonate. Robin *et al.* (1958) showed that the [HCO_3^-] of the c.s.f. does not change rapidly, and the observations reported here supplement their findings by extending the time scale from hours to days. If pH (or pCO_2) affect respiration through actions at more than one site, e.g. arterial blood and c.s.f. (Loeschcke, Koepchen & Gertz, 1958), it appears that respiratory changes accompanying alterations of acid–base balance might be incomplete even 5 days after the onset of the new conditions.

SUMMARY

1. In twenty-three normal subjects the pH, pCO_2 and [HCO_3^-] of arterial plasma and lumbar c.s.f. have been compared. The pH and [HCO_3^-] of the c.s.f. were always lower than those of the arterial plasma, by 0·090 of a pH unit and 2·0 m-equiv/l. respectively (mean results). The pCO_2 of the c.s.f. was always higher than that of the arterial plasma, the mean difference being 9·4 mm Hg. In six subjects there was little difference between the pCO_2 of c.s.f. and of jugular venous blood.

2. No significant differences in pH, pCO_2 and [HCO_3^-] were found between lumbar and cisternal c.s.f. in four subjects.

3. The effect of chronic acidosis on the acid–base characteristics of plasma and c.s.f. was studied in five patients with renal failure. The depression of the [HCO_3^-] in the c.s.f. from the normal was on average about half that in the plasma. In spite of an acidaemia, c.s.f. pH was always within 2 S.D. of the mean value for normal subjects.

4. The effects on the c.s.f. of an acute alkalaemia (intravenous $NaHCO_3$) was studied. In addition $NaHCO_3$ was given by mouth for a longer period (5–7 days) to five normal subjects and also to five patients with renal failure. The normal ratio of c.s.f. [HCO_3^-]:plasma [HCO_3^-] was not restored after $NaHCO_3$ administration in either the acute or the longer-term experiments. There was usually a small fall or no significant change in c.s.f. pH. This was because the increase in c.s.f. [HCO_3^-] was matched by a proportionate or slightly greater rise in pCO_2.

5. In five patients pulmonary ventilation was measured daily before and during the 5–7 days while they were receiving $NaHCO_3$. No significant change in ventilation was found in two normal subjects but a small fall was recorded in three patients with renal failure. If changes in c.s.f. pH affect ventilation, respiratory changes accompanying alterations of acid–base balance might be incomplete even 5 days after the onset of the new conditions.

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