THE RENAL RESPONSE IN MAN TO ACUTE EXPERIMENTAL RESPIRATORY ALKALOSIS AND ACIDOSIS [1]

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(Submitted for publication August 7, 1956; accepted December 6, 1956)

The experimental results to be presented here deal with the renal component of the multiple effects in man of acute experimental respiratory alkalosis (hyperventilation) and acidosis (CO_2 inhalation). One aim of the experiments has been to define an integrated picture of the total body response to acute respiratory acid-base disturbances. A previous paper (1) contained a description of the effects observed in the same experiments on the composition of plasma and red cells, and a quantitative estimate of the exchanges of ions and water between red cells, plasma, extracellular fluids and a phase or phases outside the chloride space ("intracellular"). In the present report consideration is given to the changes in renal excretion and hemodynamics and an attempt is made to define more clearly certain mechanisms involved. Reference should be made to the previous report (1) for data on the blood or plasma changes; only a few of these data are included here when they are directly important to interpretation and renal effects. The present findings were previously reported in abstract (2, 3).

EXPERIMENTAL PROCEDURE AND CHEMICAL METHODS

Six normal male subjects actively hyperventilated and six inhaled CO_2 as described in detail in the preceding paper (1). Following control periods of 47 to 74 minutes' duration, hyperventilation was carried out for approximately 30 minutes in 5 of the 6 experiments, and for twice that period in the last experiment; 7.5 to 7.7 per cent CO_2 in air or oxygen was inhaled for 21 to 30 minutes. Measurements were continued in both types of experiments during subsequent recovery periods which ended 97 to 145 minutes after onset of the stimulus (designated time zero). Standard water loading was carried out before the experiments and continued throughout with water given in amounts equivalent to urine excreted. In respiratory acidosis a neutral or slightly alkaline control urine was considered desirable to facilitate observation of renal effects. Accordingly, in experiments 1 to 5 inclusive, the subjects were given 4.2 gm. $NaHCO_3$ (50 mEq.) by mouth at -95 to -150 minutes. As a control, in the sixth experiment NaCl was substituted for the $NaHCO_3$ and this experiment is not included in statistical analyses. Four additional control experiments were done in which the $NaHCO_3$ load was given, and observations were made for the usual experimental time (but with no respiratory stimulus) to indicate the effect of the loading procedure alone.

Renal clearances were determined by standard techniques and chemical methods (4, 5), with bladder catheterization and appropriate anaerobic collection of urine to prevent loss of CO_2. Changes in glomerular filtration rate were estimated from changes in endogenous creatinine clearance and effective renal plasma flow from p-aminohippurate (PAH) clearance.[5] Following an equilibration period of at least 45 minutes urine was collected for 3 periods before, 1 to 4 periods during, and 3 to 4 periods after the application of the stimulus (hyperventilation or CO_2 inhalation).

Total CO_2 was determined in the anaerobically collected urine by the manometric method of Van Slyke and Sendroy (6), urine pH at 37° C by means of the photocolorimetric method of Van Slyke, Weisiger, and Van Slyke (7), sodium and potassium with a Barclay internal standard flame photometer (8), chloride by the

[1] Laboratory facilities were aided by grants from the National Heart Institute of the United States Public Health Service (Grants H-405 and H-340), the Life Insurance Medical Research Fund, and the C. Mahlon Kline Fund for Development in the Department of Medicine.

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[5] Excretion of anionic PAH^- in itself has some effect on urinary acid-base pattern. Administration was, however, at the same slow rate during both control and experimental periods and there were no significant *changes* in PAH excretion during either type of respiratory stimulus, when urinary acid-base changes were maximal. PAH could also form a buffer pair, but because it would be a strong acid buffer ($pK' = 3.83$) (13), such an effect must be very small.

Volhard-Harvey method (9), ammonia by the method of Folin and Bell (10) using a Klett-Summerson photometer, phosphate by the method of Lowry and Lopez (11), and titratable acidity by titrating to pH 7.4. The bicarbonate concentration was calculated from the total CO_2 content and pH of each urine specimen by use of factors for CO_2 solubility and pK′ in urine as functions of urinary total cation concentration, derived from Sendroy, Seelig, and Van Slyke (12).

Methods of blood sampling and analyses were described in the previous paper (1).

CALCULATIONS

Urinary electrolytes in microequivalents per minute (μEq. per min.) are presented as excretion rates (UV) rather than clearances, thus permitting immediate comparison of cation-anion equivalents. The cations determined were sodium, potassium, and ammonium; the anions were chloride, bicarbonate, and (in part) phosphate.

Magnitude of acid-base disturbances (ΔHCO_{3er}^-). Under conditions termed a "steady state" the rate at which carbon dioxide from cellular metabolism is added to the extracellular fluid equals the rate at which it is lost from the body, and there is no resulting acid-base effect on the extracellular fluid. When the pulmonary component is disturbed, as by hyperventilation or CO_2 inhalation, a net quantity of CO_2 is removed from or added to the extracellular fluid. An acid-base effect is exerted by shifting the following relationship toward either the left or right:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad (1)$$

This disturbance may be expressed in terms of equivalents as a change in HCO_3^-, and this change is proposed for the purposes of this paper as an indication of the magnitude of the acid-base disturbance. ΔHCO_{3er}^- is defined as the change in total amount of bicarbonate in the extracellular fluid (plasma plus interstitial fluid) and in the red cells. It is desirable to include the red cells since they are intimately related by the chloride shift to the acid-base changes of respiratory disturbances. The method of determination, together with observed ΔHCO_{3er}^- in the individual experiments, was given for a different purpose in the portion of the work previously published (1).

From Equation 1 it is evident that a change in H^+ equivalent to that in HCO_3^- must initially occur. However, at pH ranges compatible with life, free hydrogen ion *concentration* is always insignificant compared to the other ions. Accordingly, "buffering" mechanisms must accept the hydrogen ion in one type of disturbances or furnish it in the other.[6]

[6] The role of such mechanisms was estimated quantitatively, and it was noted that participation of some phase of body fluid outside the blood and typical interstitial fluid appears in these particular experiments to account for about two-thirds of the buffering of the hydrogen ion disturbance that would otherwise be present in the extracellular fluid (1).

Changes in rate of urinary hydrogen ion excretion (ΔUV_{H^+}). For the purpose of this paper a quantitative index of rate of H^+ excretion is defined as the sum of three components: NH_4^+ output plus titratable acid minus the HCO_3^- output. In the case of an alkaline urine the rate is a negative quantity dependent chiefly on the bicarbonate output while for urine of neutral or slightly acid pH values, all three terms are significant fractions of the total. Excretion of bicarbonate is equivalent in acid-base effect to the addition of hydrogen ion to the body and this method of calculating UV_{H^+} eliminates the necessity of treating HCO_3^- output as a separate factor. It is frequently not possible to distinguish, in the case of two separate body fluids, transfer of H^+ in one direction from transfer of HCO_3^- in the opposite direction.

In order to assess the rate of renal acid-base compensation to the respiratory disturbance it is desirable to consider the difference between UV_{H^+} observed and the UV_{H^+} which would have been present at the control rate. The *change* in urinary hydrogen ion excretion is therefore determined, thus,

$$\Delta UV_{H^+} = \Delta UV_{NH_4^+} + \Delta UV_{TA} - \Delta UV_{HCO_3^-} \qquad (2)$$

This consideration of ΔUV_{H^+} rather than UV_{H^+} in absolute terms also avoids arbitrary decisions on what constitutes a "neutral" urine as related to an extracellular fluid pH about 7.4 and a usual dietary intake and metabolism which, uncompensated, would produce a metabolic acidosis.

It should be noted that under these experimental conditions, once hyperventilation or CO_2 inhalation ceases the acid-base disturbance is rapidly corrected by respiratory adjustments. Therefore the most meaningful indications of urinary adjustments appear to be the peak ΔUV_{H^+} achieved and the cumulative change to the time the respiratory stimulus was discontinued.

RESULTS

The results are presented in Tables I A, I B, II and III and in Figures 1 through 4 and were evaluated by standard statistical methods. The average control data are included in the figures and the average changes, variability (standard error) and probability of chance occurrence are shown below the graphic part of each figure. Changes in urinary excretion rates during respiratory alkalosis or acidosis as mentioned hereafter are the mean change (from control rates) observed in the last urine collection period during hyperventilation or CO_2 inhalation.

Respiratory alkalosis

The magnitude of the acid-base disturbance was indicated by an average ΔHCO_{3er}^- of − 135 mEq. observed at the end of the period of hyperventila-

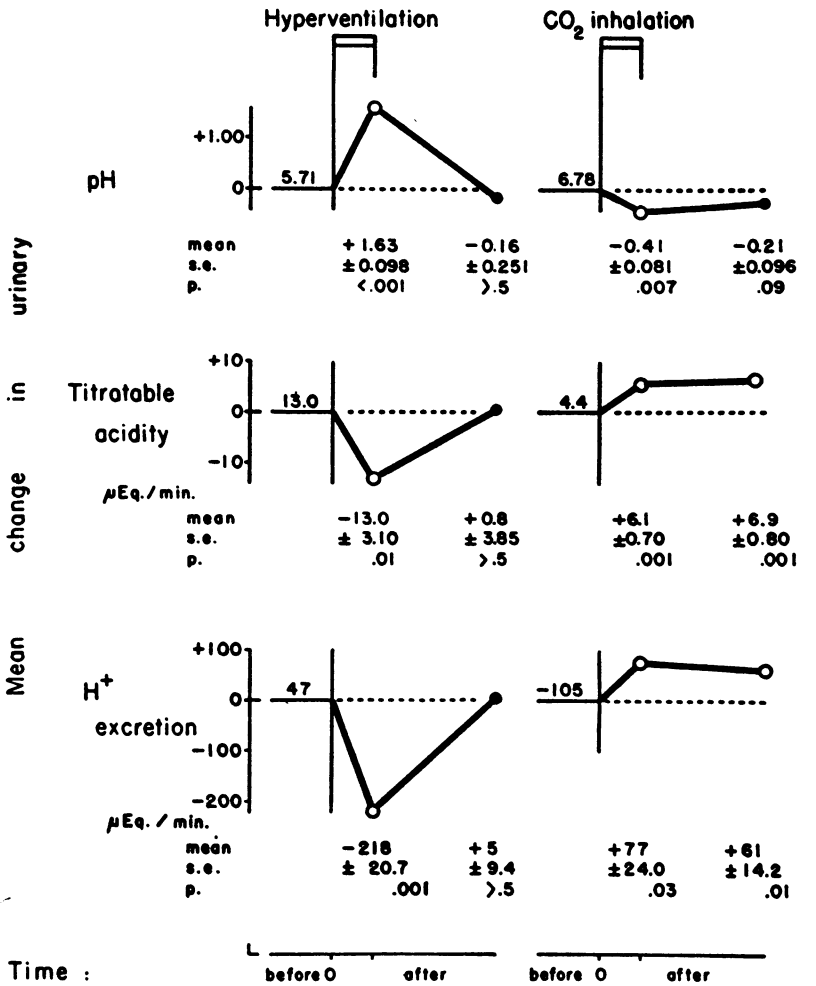

FIG. 1. ACUTE RESPIRATORY ALKALOSIS AND ACIDOSIS: MEAN CHANGES IN URINARY pH AND THE EXCRETION OF TITRATABLE ACID AND HYDROGEN ION

The mean for each group of changes from the individual mean control values is plotted for the end of the period of stimulus and the end of the experiment. The values for the mean change, its standard error, and the probability of chance occurrence are given below the curves. The mean changes that are statistically significant ($p = 0.05$ or less) are represented by open circles. The abscissae represent time before, during, and after the stimulus. The mean of the control values is given on the horizontal axis. Hydrogen ion excretion is defined as the sum of outputs of ammonium plus titratable acidity minus bicarbonate (see Equation 2 in text).

tion. The rate of renal adjustment to the disturbance by retaining H^+ ion as compared to control H^+ output (ΔUV_{H^+} by Equation 2) averaged 218 μEq. per minute for the final period during hyperventilation. During the 30 minutes of the stimulus an average of 5.9 mEq. H^+ had been retained in this way. During hyperventilation the pH of the urine rose (mean = + 1.63 pH units) and titratable acidity fell (− 13.0 μEq. per min.), both returning to the control values during the recovery period after hyperventilation. Bicarbonate excretion was markedly increased (+ 183 μEq. per min.) and ammonium ion excretion decreased (− 30 μEq. per min.); each subsequently re-

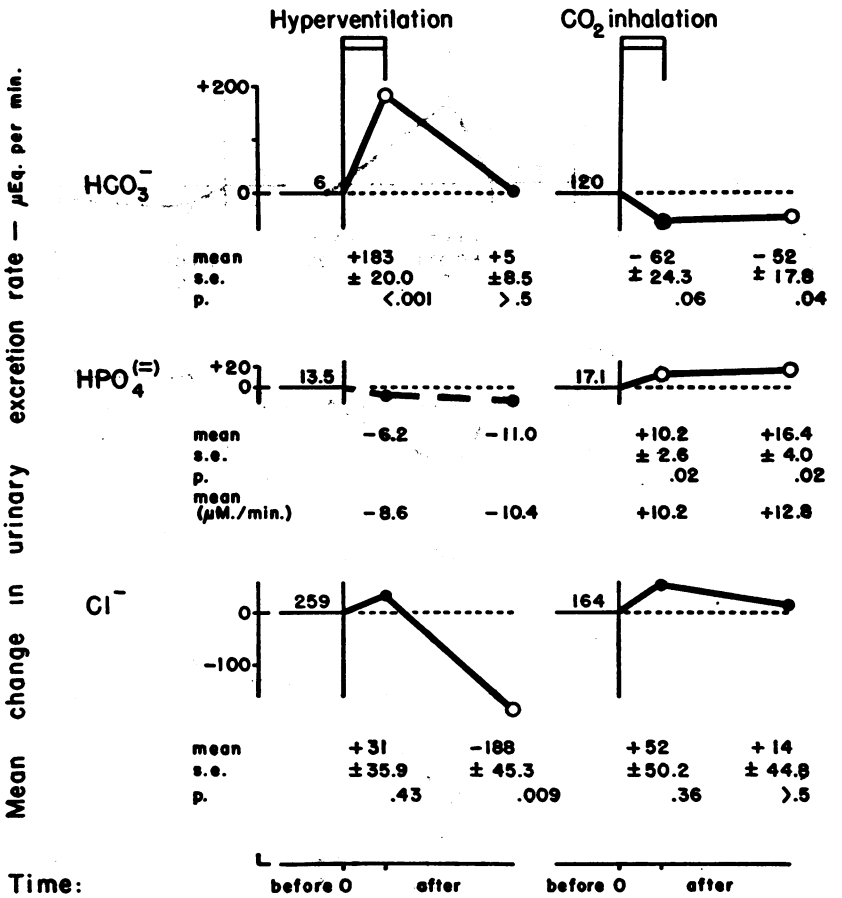

FIG. 2. ACUTE RESPIRATORY ALKALOSIS AND ACIDOSIS: MEAN CHANGES IN THE URINARY EXCRETION RATES OF ANIONS

The data are presented as in Figure 1. Since phosphate was measured in only two of the hyperventilation experiments, it is shown with a dotted line and statistical analysis omitted. The symbol $HPO_4^{(=)}$ indicates phosphate both as $HPO_4^=$ and $H_2PO_4^-$.

turned to control rates. Potassium excretion increased markedly (+ 183 μEq. per min.), while neither sodium nor chloride excretion showed a statistically significant change. In the recovery period excretion rates fell significantly below control for each of these ions (mean changes in rate per min.: K^+ − 71 μEq., Na^+ − 155 μEq., Cl^- − 188 μEq.).

Respiratory acidosis

It is clearly shown by comparison of the magnitude of the estimated acid-base disturbance ($\Delta HCO_{3er}^- = 26$ mEq.), or of plasma acid-base data (1), that CO_2 inhalation was a milder acid-base disturbance than hyperventilation. It is difficult to achieve a more severe acute experimental respiratory acidosis without undesirable side effects. Changes in urinary findings were correspondingly smaller during CO_2 inhalation than those observed during hyperventilation. ΔUV_{H^+} averaged 77 μEq. per minute and cumulative H^+ eliminated during the stimulus was 1.9 mEq. Urinary pH fell (− 0.41 pH units) and titratable acidity increased (+ 6.1 μEq. per min.). Bicarbonate excretion decreased (− 62 μEq. per min.) in spite of a considerable increase in filtered load that resulted from the increased plasma concentration during CO_2 inhalation. The change in bicarbonate reabsorption (+ 310 μEq. per min.) is accordingly significant ($p = 0.03$). Thus a

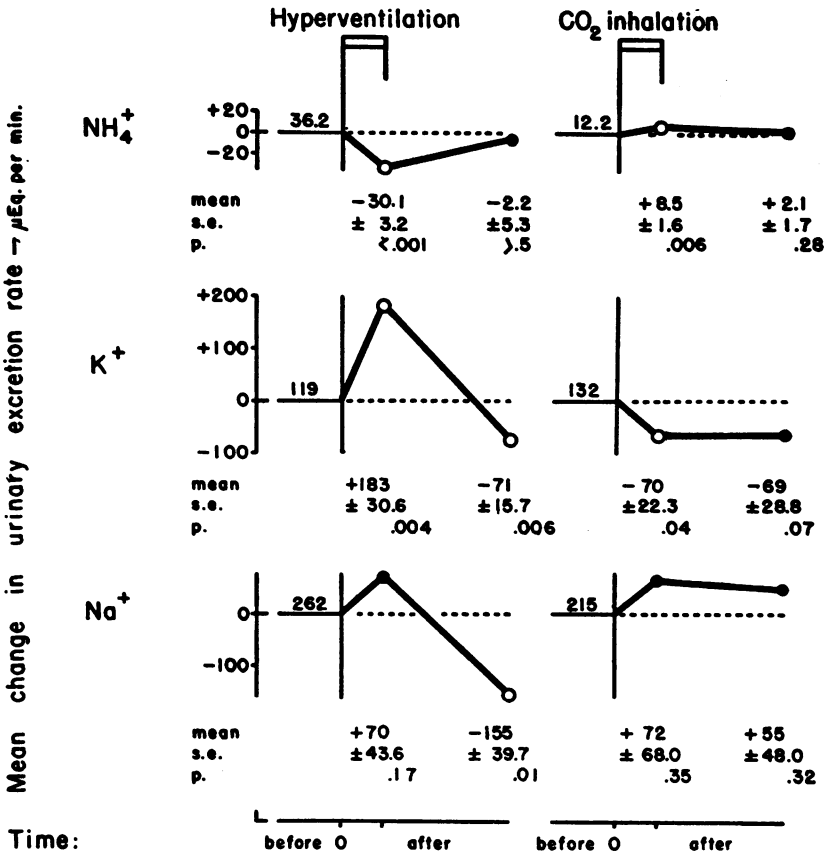

FIG. 3. ACUTE RESPIRATORY ALKALOSIS AND ACIDOSIS: MEAN CHANGES IN THE URINARY EXCRETION RATES OF CATIONS

The data are presented as in Figure 1.

real physiologic response in bicarbonate regulation is evident, although if changes in excretion alone are considered the results just fail ($p = 0.06$) to show "statistical significance." Excretion of ammonium ion increased (+ 8.5 μEq. per min.) and that of potassium decreased (− 70 μEq. per min.). Neither sodium nor chloride output showed statistically significant change. Phosphate excretion was increased (+ 10 μEq. per min.).

The small oral dose of sodium bicarbonate given preceding the respiratory acidosis experiments established a "baseline" (a neutral or alkaline urine) upon which the effect of the CO_2 inhalation could be more readily determined. Effects of the bicarbonate dose are evident in differences between the average control values in the respiratory alkalosis and acidosis experiments as shown in Figures 1 to 4. Four additional experiments

	PLASMA pH	URINARY HCO_3^- EXCRETION	TUBULAR HCO_3^- REABSORPTION	PLASMA pCO_2
RESPIRATORY ACIDOSIS	↓	↓	↑	↑
RESPIRATORY ALKALOSIS	↑	↑	↓	↓
METABOLIC ($NaHCO_3$ ADMIN.) ALKALOSIS	↑	↑	↑	↑

FIG. 4. CHANGES IN $NaHCO_3$ EXCRETION, REABSORPTION AND RELATED EXTRACELLULAR FLUID (PLASMA) FACTORS IN ACUTE RESPIRATORY ALKALOSIS AND ACIDOSIS AND IN METABOLIC ALKALOSIS

Direction of change in response to the stimulus is indicated by the arrows. For each type of disturbance the plasma HCO_3^- concentration changed in the same direction as the PCO_2. The rate of filtration of HCO_3^- (or HCO_3^- load) also changed in this direction.

TABLE I A

Respiratory alkalosis: Effects of hyperventilation on urinary pH, titratable acidity, and excretion of electrolytes

Expt. and duration stimulus in min.	Time*	pH	Titr. acid.	HCO_3^-	Cl^-	NH_4^+	Na^+	K^+
	min.		*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*
1	− 48							
	0	6.3		17	245	26	217	139
29	+ 29	7.8		251	242	7	218	414
	+ 61	7.6		104	79	8	65	189
	+ 89	7.2		123	64	13	90	151
	+118	7.2		64	56	10	89	97
3	− 53							
	− 34	5.70	10	8	195	42	230	146
	− 20	5.80	6	11	165	38	210	127
	0	5.88	5	11	172	35	225	123
30	+ 14	7.00	0	111	325	19	520	232
	+ 30	7.38	0	184	240	4	420	272
	+ 45	7.01	0	45	81	2	147	143
	+ 60	5.7	12	2	76	34	163	126
	+ 90	5.5	10	2	37	34	139	37
	+121	5.2	17	0	34	50	143	22
4	− 74							
	− 53	5.30	22	1	135	48	127	84
	− 37	5.39	18	2	116	54	104	92
	0	5.40	18	1	80	48	93	60
37	+ 22	6.77	4	64	170	24	160	167
	+ 37	7.20	0	171	251	13	214	332
	+ 55	—	4	16	72	5	55	130
	+ 86	5.34	10	0	39	27	31	60
	+117	5.2	15	0	34	31	32	47

Expt. and duration stimulus in min.	Time*	pH	Titr. acid.	HCO_3^-	Cl^-	Phosphate		NH_4^+	Na^+	K^+
	min.		*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μM per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*
5	− 47									
	− 33	5.57	23	4	187	23	22	36	252	105
	− 17	5.62	20	8	193	22	21	35	252	99
	0	5.62	22	7	212	21	20	35	263	99
32	+ 16	6.64	5	79	335	28	20	20	455	178
	+ 32	7.28	0	166	305	14	8	5	440	208
	+ 53	7.21	0	80	101	2.1	1.2	5	143	189
	+ 83	6.16	7	14	110	2.4	2.0	22	143	108
	+117	5.60	11	5	70	3.1	2.9	39	116	65
6	− 49									
	− 34	5.32	9	1	565			39	520	148
	− 19	5.40	10	2	640			47	580	168
	0	5.62	6	3	510			45	455	144
27	+ 16	7.04	0	132	610			19	600	292
	+ 30	7.35	0	248	485			6	500	370
	+ 51	6.68	0	36	325			14	258	186
	+ 82	5.55	5	2	285			34	288	57
	+116	5.22	9	0	176			41	178	38
7	− 55									
	− 38	6.24	4	3	258	4.6	4.7	18	278	109
	− 23	5.78	7	2	255	4.7	4.3	22	253	—
	0	5.28	15	1	250	5.0	4.8	31	220	118
58	+ 15	6.38	4	29	267	5.5	4.3	22	274	163
	+ 27	6.91	0	121	289	2.5	1.6	4	330	228
	+ 40	7.01	0	128	280	1.3	0.8	2	280	233
	+ 58	7.06	0	117	218	0.5	0.3	2	202	220
	+ 77	6.84	0	36	138	0.4	0.3	4	98	135
	+108	5.12	11	0	86	0.5	0.3	24	92	52
	+144	4.86	17	0	56	1.9	1.9	33	83	24

* Data are expressed per individual periods which end at the time indicated, measured from the start of hyperventilation. Values obtained during hyperventilation are separated by horizontal single lines.

TABLE I B

Respiratory acidosis: Effects of CO_2 inhalation on urinary pH, titratable acidity and excretion of electrolytes

Expt. and duration stimulus in min.	Time*	pH	Titr. acid.	HCO_3^-	Cl^-	Phosphate		NH_4^+	Na^+	K^+
	min.		*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μM per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*
1	− 37									
	− 25	7.00	7	56	296	29	18	23	352	83
	− 13	7.06	—	58	222	27	16	—	275	69
	+ 4	6.91	6	70	227	34	22	26	300	83
30	+ 14	6.50	6	50	243	36	27	39	373	49
	+ 33	6.34	14	60	469	48	39	36	634	39
	+ 48	6.52	9	74	400	47	35	22	592	42
	+ 68	6.52	12	25	292	38	28	26	400	27
	+ 97	6.18	21	9	217	36	30	42	311	16
2	− 57		†							
	− 41	6.93	4	245	164	23	15	10	275	199
	− 17	6.86	4	221	142	23	15	10	258	177
	− 2	6.83	—	181	133	—	—	9	235	156
27	+ 14	6.74	6	152	138	24	16	13	237	113
	+ 30	6.49	9	84	123	27	20	14	190	74
	+ 45	6.69	8	106	151	34	24	16	240	84
	+ 67	6.57	9	95	112	30	22	17	222	73
	+ 90	6.60	11	125	120	37	27	16	264	125
	+121	6.72	10	130	124	40	28	13	239	107
3	− 47		†							
	− 32	6.61	4	59	100	14	10	14	167	48
	− 16	6.82	2	84	104	9	6	11	182	64
	− 1	6.76	2	109	135	10	6	10	233	82
29	+ 13	6.97	2	104	152	14	9	9	252	85
	+ 29	6.59	7	70	214	22	16	17	282	58
	+ 44	6.64	7	67	209	24	17	14	280	64
	+ 63	6.73	8	111	317	31	21	12	425	90
	+ 97	6.73	8	124	352	33	23	12	480	100
	+129	6.73	9	97	305	37	25	13	415	92

Expt. and duration stimulus in min.	Time*	pH	Titr. acid.	HCO_3^-	Cl^-	Phosphate		NH_4^+	Na^+	K^+
	min.		*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*	*μM per min.*	*μEq. per min.*	*μEq. per min.*	*μEq. per min.*
4	− 47									
	− 32	6.72	4	116	137	4	3	9	186	129
	− 17	6.78	4	137	143	5	4	7	197	167
	− 2	6.73	6	119	169	6	4	7	216	155
21	+ 22	6.29	12	44	170	10	8	17	191	83
	+ 37	6.40	9	53	161	10	8	16	238	55
	+ 53	6.45	11	56	153	9	7	9	245	47
	+ 82	6.46	6	56	112	10	7	13	211	32
	+111	6.29	10	41	101	18	15	15	173	23
5	− 50									
	− 36	6.68	3	139	182	18	12	8	211	221
	− 20	6.58	2	111	158	15	11	7	181	189
	0	6.52	7	96	143	17	12	9	173	164
30	+ 15	6.46	6	73	124	22	17	9	157	116
	+ 30	6.17	11	29	100	29	24	20	138	58
	+ 44	6.27	20	36	150	43	35	20	193	68
	+ 61	6.45	18	53	144	46	36	13	206	86
	+ 92	6.51	16	67	160	51	38	12	250	82
	+122	6.57	14	62	135	39	28	8	223	62
6‡	− 51									
	− 35	5.88	12	10	56	11	10	40	33	105
	− 19	5.88	11	11	48	12	11	32	50	107
	0	5.94	13	14	58	14	13	32	56	118
22	+ 24	5.97	14	21	139	23	21	37	165	95
	+ 42	5.89	22	14	144	27	24	36	177	99
	+ 60	6.01	11	17	155	30	26	32	192	105
	+ 96	5.88	22	13	151	30	27	40	151	117
	+129	5.79	23	8	86	28	26	44	78	111

* Data are expressed per individual periods which end at the time indicated, measured from the start of CO_2 inhalation. Values obtained during CO_2 inhalation are separated by horizontal single lines.

† Titratable acidity calculated from phosphate in Experiments 2 and 3.

‡ Experiment 6 is not included in statistical analyses. This experiment was done as a control, the urine being initially acid as explained in the text.

TABLE II

Respiratory alkalosis and acidosis: Calculated extracellular acid-base disturbance ($\Delta HCO_3^-{}_{ec}$) and renal compensation (ΔUV_{H^+})† at end of respiratory stimulus*

A. Respiratory alkalosis (hyperventilation)				B. Respiratory acidosis (CO_2 inhalation)			
		ΔUV_{H^+}				ΔUV_{H^+}	
Expt.	$\Delta HCO_3^-{}_{ec}$	Rate	Cumulative	Expt.	$\Delta HCO_3^-{}_{ec}$	Rate	Cumulative
	mEq.	*μEq. per min.*	*mEq.*		*mEq.*	*μEq. per min.*	*mEq.*
3	−141	−215	−5.0	1	+46	+ 20	+0.64
4	−189	−226	−5.6	2	+12	+142	+4.3
5	−125	−212	−5.0	3	+38	+ 23	+0.16
6	−152	−292	−6.7	4	+ 2	+ 97	+2.3
7	− 67	−146	−7.0	5	+31	+105	+2.2
Mean	−135	−218	−5.9	Mean	+26	+ 77	+1.9

* $\Delta HCO_3^-{}_{ec}$ indicates the total change in bicarbonate of the extracellular fluid (plasma plus interstitial fluid) and of the red cells (1).

† ΔUV_{H^+} indicates the change from control in urinary hydrogen ion excretion defined as the sum of ammonium plus titratable acid minus bicarbonate output (see Equation 2 in text).

were done without any disturbance of respiration to evaluate the effect of the oral bicarbonate alone. These experiments also provided a control for the acidosis series with respect to the effects of the diurnal "tide" and the water loading procedure. While slight apparent changes were present at the times that would correspond to the respiratory stimulus, none of them was statistically significant. Changes during the stimulus in the respiratory acidosis series which are significantly different from the preceding control values also differ significantly from the slight alterations at corresponding times in the control series. This is true for all of the variables except urinary pH and K^+ excretion, the differences of which were not quite significant at the 5 per cent level. During the comparatively longer recovery portion of the experiments, a tendency in the acidosis series to disappearance of the effects of the oral bicarbonate on the "baseline" would be indistinguishable from persistence of acidification of the urine as a compensatory mechanism to the respiratory disturbance. Accordingly, discussion of changes late in recovery is limited to respiratory alkalosis. Results are not reported in detail for the control series.

Renal hemodynamics and urinary volume

Measurements made of effective renal plasma flow, glomerular filtration rate, and rates of urine flow are not reported in detail. Significant changes were observed only with hyperventilation. Effective renal plasma flow was depressed from control at the end of these experiments, a change correlating with the excretion rate of sodium and chloride which were also significantly depressed at this time. Glomerular filtration rate was also decreased significantly at the end of the experiments, but also decreased somewhat during the hyperventilation, at a time when excretion of sodium and chloride and effective plasma flow were not significantly altered and if anything were a little increased. Changes in urine flow were probably more closely related to the water loading than to the experimental procedure.

DISCUSSION

Observation of renal acid-base adjustment

The kidney responds promptly to primary respiratory alterations of acid-base equilibrium. The renal adjustment is not a simple correction of the abnormality present, but may be considered as eventually producing an opposing "metabolic" (as contrasted to "respiratory") disturbance which may be measured as a change in the rate of hydrogen ion excretion (ΔUV_{H^+}). An increase in UV_{H^+} is equivalent to an increase in buffer base in the body. Singer and Hastings (14) suggested certain practical advantages in focussing attention on the buffer base concentration as a quantitative index of the metabolic or non-respiratory factor in acid-base equilibrium and pointed out that a pure respiratory disturbance (before various com-

TABLE III

Respiratory alkalosis and acidosis: Renal filtration, reabsorption and excretion of bicarbonate

Expt.	Time*	Urine flow (ml. per min.)	GFR (ml. per min.)	Plasma pH	Plasma PCO_2 (mm. Hg)	Plasma HCO_3^-† (mEq. per L.)	HCO_3^- Filt. (mEq. per min.)	HCO_3^- Excr. (mEq. per min.)	HCO_3^- Reabsorbed (mEq. per min.)	HCO_3^- Reabsorbed (mEq. per L. filtrate)
				A. Respiratory alkalosis—hyperventilation						
3	C*	10.4	125	7.38	43	24.9	3.11	.010	3.10	24.82
	S	5.0	109	7.62	19	19.2	2.09	.184	1.91	17.52
	R	1.9	124	7.40	42	25.4	3.15	0	3.15	25.42
4	C	6.6	104	7.35	43	23.6	2.45	.001	2.45	23.58
	S	6.2	108	7.65	15	16.5	1.78	.171	1.61	14.92
	R	0.5	80	7.43	37	24.4	1.95	0	1.95	24.41
5	C	12.1	122	7.39	43	25.6	3.13	.006	3.12	25.58
	S	5.3	87	7.63	19	20.2	1.76	.166	1.59	18.29
	R	9.3	118	7.44	39	25.7	3.03	.005	3.03	25.67
6	C	7.5	109	7.39	43	25.3	2.76	.002	2.76	25.28
	S	7.8	86	7.66	16	17.9	1.54	.248	1.29	15.00
	R	3.8	96	7.43	37	24.2	2.32	0	2.32	24.20
7	C	1.6	132	7.30	44	24.9	3.29	.002	3.29	24.89
	S	5.9	108	7.56	25	22.2	2.40	.117	2.28	21.13
	R	3.9	109	7.39	42	24.9	2.71	0	2.71	24.89
				B. Respiratory acidosis—CO_2 inhalation						
1	C	3.0	139	7.40	46	27.5	3.82	.061	3.76	27.05
	S	17.2	151	7.35	54	29.9	4.52	.060	4.46	29.53
	R	4.0	135	7.45	40	27.0	3.64	.010	3.64	26.97
2	C	18.2	126	7.46	40	27.8	3.50	.216	3.29	26.11
	S	16.4	127	7.40	47	28.7	3.64	.123	3.52	27.71
	R	17.2	131	7.43	40	26.5	3.47	.125	3.35	25.57
3	C	11.1	111	7.50	34	25.5	2.83	.084	2.75	24.76
	S	10.6	114	7.37	48	27.1	3.09	.070	3.02	26.49
	R	13.6	117	7.44	37	24.4	2.86	.111	2.74	23.42
4	C	16.7	115	7.44	41	26.7	3.07	.124	2.95	25.63
	S	14.8	117	7.34	51	27.0	3.16	.044	3.12	26.68
	R	15.8	116	7.48	34	24.6	2.85	.056	2.80	24.13
5	C	16.8	108	7.44	38	25.3	2.73	.115	2.62	24.26
	S	13.1	107	7.33	52	26.5	2.84	.029	2.81	26.18
	R	14.1	106	7.44	26	24.2	2.57	.053	2.51	23.68
6‡	C	12.1	102	7.32	49	24.7	2.52	.012	2.51	24.60
	S	15.3	110	7.26	62	27.1	2.98	.021	2.96	26.90
	R	14.7	106	7.37	45	25.5	2.70	.013	2.69	25.38

* Time of individual periods and respiratory stimuli is given in Table I A and I B.
C denotes average of the control periods.
S denotes the last period during the respiratory stimulus.
R denotes the last period for which complete data were available during recovery from the effects of the stimulus.

† The plasma concentration of HCO_3^- given and used to calculate HCO_3^- filtered is that observed (often at the end of the period) rather than an interpolated value for mid-period. No correction is made for serum water or Donnan factor.

‡ Experiment 6 during CO_2 inhalation was done as a control, the urine being initially acid as explained in the text.

pensations) causes no change in whole blood buffer base. Fuller and MacLeod (15) have calculated the rate of "total H^+ secretion" by adding HCO_3^- *reabsorption* to titratable acidity plus ammonium excretion rather than by subtracting HCO_3^- *excretion* as we do in calculating UV_{H^+}. The resulting index is quite different since our index indicates the net *effective acid-base adjust-*

ment accomplished by the over-all process of urine formation while theirs relates to the specific process of H^+ secretion by the tubular cells.[7]

In *respiratory alkalosis* the characteristic response is a decrease in H^+ output, measured principally by an increase of HCO_3^- with fixed cation in an alkaline urine (17–22). Associated with this is a decrease in output of ammonia and titratable acid. The resultant effect on total body fluids is a loss of buffer base, a further reduction of the already lowered HCO_3^- concentration and a return of pH toward the normal range. The accompanying predominant change in excretion of "fixed" ion in the first half hour of acute experiments is increased K^+ loss, rather than change in Na^+ or Cl^-. The duration of the experiments was such that cumulative excretion while the stimulus persisted had very little effect in changing extracellular or total body fluid buffer base. The renal compensation was therefore small compared to the rapid sharing of the effects of the stimulus by the various "buffer" mechanisms of the body previously estimated in detail (1). Calculations based on the data of other workers (23, 24) indicate that in more prolonged respiratory disturbances the major part of ΔHCO_{3er}^- may be compensated by cumulative urinary changes.

Renal compensation for acute respiratory alkalosis appears to be less efficient than that for acute metabolic alkalosis of the "electrolyte addition" type. In seven experiments in which we gave rapid intravenous infusions of hypertonic sodium bicarbonate (25, 26) the total dose of bicarbonate given was of the same order of magnitude as the ΔHCO_{3er}^- observed in respiratory alkalosis reported here. Yet, within the same time, cumulative ΔUV_{H^+} averaged 19.6 mEq., indicating more than three times the comparable renal compensation during respiratory alkalosis.[8] The difference may be related to the fact that this type of metabolic alkalosis (a simple excess of sodium and bicarbonate) may be corrected by the renal excretion of the ions present in excess.

The characteristic changes in *respiratory acidosis* are the opposite of those described for respiratory alkalosis (15, 17, 27). There is an increase in excretion rates of H^+, titratable acid and ammonia and a decrease in excretion of bicarbonate with fixed cation, especially potassium. The urine becomes more acid. Since the acid-base disturbance of acute experimental CO_2 inhalation is considerably milder than that of hyperventilation, the urinary changes are much smaller in absolute terms. Relative to the estimated acid-base disturbance (ΔHCO_{3er}^-), however, the renal response appears to be of the same order of magnitude. When the experiments were planned we postulated that it would be difficult to detect an increase in UV_{H^+} if the control urine were already acid. If the "basal" state of the kidney involves compensation for the tendency of the usual diet to produce a slight metabolic acidosis, it would scarcely be surprising that an acute respiratory acidosis of mild degree should fail to bring about a further detectable increase in UV_{H^+}. We believe that this is the explanation for the lack of response in urinary acid-base factors noted by Longson and Mills (28), and in urinary output of sodium, potassium and chloride by other workers (29), during acute CO_2 inhalation in man. Similarly, in our Experiment 6, with NaCl substituted for the small pre-medication dose of $NaHCO_3$ (and a control urine pH of 5.9) there was no detectable change in UV_{H^+}. In spite of the acid control urines, it seems probable that a renal tubular response could have been found in the experiments of Longson and Mills (28) had changes in filtered load and reabsorption of bi-

[7] The use of the index proposed by these authors involves the assumption that the basic tubular process of H^+ secretion is involved in the entire quantity of HCO_3^- reabsorbed. This view is presently held by most workers, as they point out, but it has also been recently challenged (16).

[8] For the bicarbonate administration studies renal adjustment was calculated by an alternative approximation rather than by ΔUV_{H^+} as defined in this paper. From the laws of buffer action and electroneutrality it follows that changes in UV_{H^+} must be accompanied by an equal change in excretion of fixed cation minus fixed anion of opposite algebraic sign. Under many circumstances, including our own experimental conditions, a fairly satisfactory approximation of ΔUV_{H^+} can be derived from changes in excretion rates of the major fixed ions of urine, as $Na^+ + K^+ - Cl^-$. Expression of the urinary adjustment in these alternative terms directs attention to the effect on body fluid content of the major fixed ions, which may be convenient in consideration of acid-base changes there. Use of this approximation during hyperventilation indicates an average change of $+222$ μEq. per min., surprisingly close to the ΔUV_{H^+} of -218 μEq. per min. by the other method.

carbonate been determined rather than in excretion alone. Data of Denton, Maxwell, McDonald, Munro, and Williams (30) during CO_2 inhalation in sheep indicate a marked rise in HCO_3^- reabsorption, although, like Longson and Mills, they observed no change in rate of urinary excretion of HCO_3^-. In contrast to these negative urinary results other workers have found characteristic changes in urinary acid-base factors in acute respiratory acidosis in dogs (15, 17, 31).[9] Where given, control urinary pH values in these experiments were close to 7.0 or above. We observed significant urinary changes in the five subjects who were given the preceding oral dose of $NaHCO_3$, and in whom the control urine pH was also approximately neutral.

Other factors influence the characteristic renal response observed during respiratory acid-base disturbances. For example, the typical urinary response to respiratory alkalosis is lacking in subjects who are in a state of NaCl depletion (18, 20). It is to be expected that pre-existing disturbances of the circulation or fluid and electrolyte balance, endocrine factors, and kidney disease may alter the characteristic changes that have been defined.

In more prolonged respiratory disturbances (for example of four or five days' duration) the ability of the kidney to compensate appears increased over that seen initially (32). Ammonium excretion is likely to constitute a larger fraction of the renal response to more prolonged acidosis. Although NH_4^+ output begins to rise within a few minutes of onset of acidosis, it does not approach maximal rates for some hours or days (33).

The urinary findings in different phases of respiratory acid-base disturbances

It must be emphasized that the characteristic combination of urinary changes described above is typical only of the "displacement" phase of the respiratory disturbance. While changes in urinary rates of H^+ excretion persist they result in a progressive increase in the degree of metabolic acidosis or alkalosis which compensates in part for the respiratory disturbance. If the abnormal level of PCO_2 persists for periods much longer than the duration of the present experiments, eventually a point will be reached where the secondary change in extracellular buffer base and other chemical changes have restored the pH to a level of stability in or closer to the normal range. In the ensuing "steady state" phase of the disturbance renal compensation ceases, in the sense that no further progressive change is produced in buffer base of body fluids. Output of H^+ then reflects the dietary intake and other physiological processes, as it does in a state of normal respiration and PCO_2. Finally, during the "recovery" phase of a chronic respiratory acid-base disturbance, when PCO_2 is returning toward normal, renal compensation serves to restore the extracellular buffer base to normal. Changes are therefore the precise opposite of those described for the displacement phase: increase in UV_{H^+} in chronic respiratory alkalosis, and decrease in chronic respiratory acidosis. Thus in chronic respiratory disturbances a temporary increase in the respiratory difficulty (equivalent to an additional "displacement" phase) will be accompanied by reappearance of characteristic urinary changes; a temporary decrease in the respiratory difficulty (equivalent to a partial "recovery" phase) will cause the opposite type of urinary changes. Such a sequence of events is quite otherwise to the situation found in metabolic acid-base disturbances. In a complete study of the displacement, stabilization, and recovery phases of ammonium chloride acidosis, Sartorius, Roemmelt, and Pitts (33) have shown that the fundamental urinary response is one of increased UV_{H^+} in all of these phases, despite serial differences in individual constituents that are also of importance. The same holds true for the opposite changes in metabolic alkalosis produced by electrolyte addition (25, 26). In acute respiratory experiments of brief duration, such as those reported here, there is no stabilization, and recovery is marked simply by a return of the urinary acid-base output toward control levels.[10] Superimposed on this return,

[9] A change is evident in the urinary data of Fuller and MacLeod (15), although their calculation of "total H^+ secretion" did not change significantly because of a fall in glomerular filtration rate and therefore in bicarbonate reabsorption. Their method of calculation showed that 90 to 98 per cent of "total H^+ secretion" was accounted for by bicarbonate reabsorption in respiratory disturbances.

[10] Fuller and MacLeod (15) reported that urinary effects of respiratory acidosis were rapidly reversible,

however, are the effects of other factors, such as diurnal fluctuations (34), the wearing off of the slight metabolic alkalosis previously induced in the subjects exposed to CO_2 inhalation, persistence of slight differences in respiration, and late effects of the imposed diuresis.

Once the "balance" between the existing respiratory disturbance and the compensatory metabolic acidosis or alkalosis (produced by the kidney) has been reached, there similarly may be nothing distinctive about the urinary excretion for individual ions except as related to the accompanying composition of plasma. For example, in one of our unpublished cases of chronic CO_2 retention with a plasma PCO_2 of 120 mm. Hg, urinary chloride excretion exceeded 40 mEq. per day, corresponding approximately to the intake, despite an extremely low plasma chloride concentration of 74 mEq. per liter. It is not surprising that the observer may erroneously conclude that renal compensations are unimportant in such disturbances if he directs his attention to the urinary composition alone. Determination of clearance rates or reabsorptive rates for acid-base factors will, however, disclose the presence of renal response.

Regulation of renal bicarbonate excretion

Change in the rate of excretion of bicarbonate was the principal anionic response of the kidney to the respiratory disturbances. In a preliminary report of the present work (3) it was stated that bicarbonate *excretion* rate correlated better with plasma pH than with other plasma factors such as PCO_2 or HCO_3^- concentration. About the same time Brazeau and Gilman (35), Dorman, Sullivan, and Pitts (36), and Relman, Etsten, and Schwartz (37) each reported studies showing that the *reabsorption* of bicarbonate was more closely related to the PCO_2 of the blood than to pH or concentration of bicarbonate. Several recent references misconstrue our data and interpretations as in disagreement with the above groups. This confusion has resulted from the failure to note the terms in which the data are reported. Examination of the directional changes given in Figure 4 will disclose that actually no disagreement exists. In our consideration of the over-all effect of the renal compensation on the body we stressed output (excretion). The figure illustrates that HCO_3^- excretion is decreased in respiratory acidosis and increased in both respiratory and metabolic alkalosis. Since both plasma PCO_2 and plasma HCO_3^- concentration move in the opposite directions in respiratory alkalosis and metabolic alkalosis, it is obvious that HCO_3^- *excretion* is better correlated with plasma pH. The three groups of investigators mentioned above, however, were interested primarily in the renal component due to active tubular processes. In studying the regulation of these processes they therefore logically stressed bicarbonate *reabsorption*. Figure 4 shows that the rate of HCO_3^- reabsorption is decreased in respiratory alkalosis but increased in metabolic alkalosis (electrolyte addition). Obviously, then, reabsorption does not correlate well with plasma pH but could be correlated (in direction of change) with either plasma bicarbonate concentration or PCO_2.[11] In experiments carefully designed to test this point the groups mentioned above found in dogs that PCO_2 was the more closely related. If our human data are used for calculation of correlation coefficients it is found that reabsorptive rate does correlate somewhat better with PCO_2 than with plasma bicarbonate concentration. Thus, it should be apparent that conclusions about changes in bicarbonate *excretion* cannot be considered as simply the opposite of changes in *reabsorption*. If the filtered load changes sufficiently, rates of reabsorption and excretion may change simultaneously in the same direction, as happened in the bicarbonate administration experiments.

Renal excretion of potassium

The predominance of changes in potassium excretion rate over those of sodium is a striking result since the sodium greatly exceeds potassium in the glomerular filtrate. At the end of either hyperventilation or CO_2 inhalation the significance of change in potassium excretion compared to con-

while hyperventilation produced lasting depression of titratable acid excretion and increase in bicarbonate excretion. These findings in anesthetized dog experiments differ from the return to control values after hyperventilation noted in humans in our studies and those of Stanbury and Thomson (20).

[11] Several workers have advanced the suggestion that this effect may be mediated through changes in pH within the tubule cells (38, 39).

trol rate clearly exceeded that of the corresponding changes in sodium excretion. Indeed in the hyperventilation experiments even the absolute magnitude of increased excretion was much greater ($K^+ + 183$ μEq. per min., $Na^+ + 70$ μEq. per min.). Since potassium is the predominant intracellular cation one might suggest that the release of potassium from body cells as a compensatory mechanism to hyperventilation is involved. A close relation between potassium and buffering action of intracellular fluid has been prominently considered since the work of Darrow and his associates (40, 41) on certain potassium deficiency states. The calculated "cellular exchanges" of potassium in our experiments (1) would affect extracellular concentration in the same direction as do the changes in urinary excretion of potassium. Thus they are in the direction opposite to that which would be required to explain the urinary findings through a change in plasma potassium concentration and secondarily in renal load. The change in potassium excretion under these circumstances might result from a reciprocal relationship between the tubular secretions of hydrogen ion and potassium as suggested by Berliner, Kennedy, and Orloff (42).

Sodium and chloride excretion.

In extracellular fluid, changes in buffer base are approximately equal to changes in $Na^+ - Cl^-$. Yet during the first half hour of respiratory acid-base disturbances those changes that did occur in sodium and chloride excretion tended to be in the same direction. Therefore urinary $Na^+ - Cl^-$ excretion showed little variation and change in fixed ions accompanying ΔUV_{H^+} was associated predominantly with K^+. The alterations in sodium and chloride excretion were not directly correlated with the continuation and withdrawal of the experimental stimuli, and were not necessarily opposite in direction in the acidosis from the alkalosis experiments. Our data therefore do not support the suggestion of Stanbury and Thomson (20) that a fall in chloride output following acute hyperventilation may represent a separate acid-base mechanism favoring conservation of "fixed acid" (Cl^-). Since these parallel changes of sodium and chloride excretion are not concerned with preserving acid-base homeostasis, some other physiological process must be involved. This might concern mechanisms of electrolyte conservation, hormonal factors, or renal hemodynamic changes. Renal plasma flow, but not glomerular filtration rate, showed a positive correlation with sodium and chloride excretion in the hyperventilation studies, while neither showed statistically significant changes with CO_2 inhalation.

Excretion of other ions

Phosphate excretion changes in two ways: as the rate of total phosphate output (in μM per min.) and as the proportion as $HPO_4^=$ or as $H_2PO_4^-$. Changes in the buffer role of phosphate as a transporter of H^+ are included in the titratable acidity, of which phosphate is an important part. This may be expressed quantitatively by the difference between the excretion rate of phosphate in μEq. per min. at the observed pH and the calculated rate in μEq. per min. that would occur if the same number of μM were excreted at a pH of 7.4. An increase in μM per min. phosphate excretion is regularly observed in respiratory acidosis (17, 30, Table I B) and a decrease in respiratory alkalosis (17, 19, 20, Table I A), but these changes are small relative to the other changes. Calculated *undetermined anion* excretion showed only very small changes in both types of experiments. It is therefore unlikely that changes in *excretion* of sulfate, lactate or organic acids are quantitatively important compared to the other changes reported.

SUMMARY

Acute respiratory alkalosis by voluntary hyperventilation for approximately thirty minutes, or acidosis by CO_2 inhalation for a similar period, were induced in normal human subjects. The urinary excretion of water and electrolytes and the acid-base pattern of the urine were observed in multiple clearance periods before, during and after the respiratory stimuli.

In *respiratory alkalosis* the kidney responded promptly by retaining hydrogen ion compared to control excretion, measured principally as an increase in output of bicarbonate with potassium. Urinary pH rose and titratable acidity, ammonium ion, and phosphate excretion fell. The potassium effect appeared to be due to renal regulation rather than secondary to systemic intracellular adjust-

ments. Chloride excretion tended to vary with that of sodium, increasing slightly during hyperventilation and then falling far below the control level.

Changes observed during *respiratory acidosis* were, for most variables, opposite in direction to those noted during hyperventilation. They were smaller in magnitude since the experimental acute respiratory acidosis by CO_2 inhalation was a milder acid-base disturbance than hyperventilation as indicated by degree of plasma changes and estimation of total extracellular acid-base disturbance. Changes in excretion of sodium and chloride were not as definite as those in other factors and were not always opposite in direction in the two types of experiment. At least part of this change (when sodium and chloride change in the *same* direction) appears not immediately concerned with acid-base homeostasis. If the urine is already acid the typical urinary changes may not be evident during acute CO_2 inhalation.

Renal mechanisms account for only a small part of the adjustments observed in experiments of short duration, but become more important with prolonged stimuli. The rate of renal acid-base compensation is considerably greater in acute extracellular alkalosis of similar magnitude induced by sodium bicarbonate administration. The urinary patterns described are typical of the "displacement" phase of respiratory disturbances. With chronic respiratory disturbances a stabilized situation may be reached in which changes are not evident in rates of urinary output of hydrogen ion except as compared to abnormalities of the acid-base composition of plasma; if "recovery" then occurs the direction of hydrogen ion excretion typical of the "displacement" phase is reversed.

The data are compatible with the finding of others that the tubular *reabsorption* of HCO_3^- is better correlated with plasma PCO_2 than with other extracellular acid-base factors. Changes in *excretion* of HCO_3^-, however, which determine the effect on the body, correlate with plasma pH and not with plasma PCO_2, if one considers both respiratory and metabolic disturbances.

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