A STUDY OF THE EFFECTS OF SULFANILAMIDE ON ACID–BASE METABOLISM [1, 2]

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That there is a reduction of the CO_2 content of the serum of patients receiving sulfanilamide was pointed out by Southworth (1). This finding has been regularly encountered by other observers. Usually hyperpnea of varying degrees is present. The development of severe acidosis is, however, very rare. That the urine becomes strongly alkaline at the same time was pointed out by Basman and Perley (2). Strauss and Southworth (3) described a large amount of fixed base in the form of bicarbonate in the urine. Marshall, Cutting and Emerson (4) demonstrated that large doses of the drug (1 or 2 grams per kgm.) cause very severe acidosis in dogs. These findings produced the inference that the change in breathing was compensatory for bicarbonate reduction in the plasma. Recently, however, Hartmann, Perley and Barnett (5) have advanced the hypothesis that the clinical and chemical findings can best be explained on the basis of an alkalosis caused by a primary hyperventilation. Their evidence was the demonstration in four subjects of a slight rise in serum pH in the presence of considerable reduction of serum bicarbonate and secretion of a strongly alkaline urine. According to this view, the removal of fixed base in urine, with consequent reduction of plasma bicarbonate, is a secondary and compensatory event. That such an adjustment may take place in response to reduction of plasma carbonic acid by hyperventilation is shown by the results of voluntary overbreathing experiments (6), although it should be noted that in these experiments the removal of bicarbonate in urine occurs in the presence of a much more extensive increase in serum pH than Hartmann found following sulfanilamide administration.

This paper presents the results of a further examination of the changes in acid-base excretion and in the electrolyte structure of the blood serum in the presence of sulfanilamide administration, and of the relationship of increased lung ventilation to these changes. These two items of inquiry were approached by different paths. The results obtained will therefore be described separately.

ACID-BASE CHANGES IN URINE AND IN BLOOD SERUM

The information sought was a description of changes in acid-base excretion in urine during periods of sulfanilamide administration sufficiently quantitative to permit correlation with measurements of alterations in the usual electrolyte structure of the serum.

Plan of study

In order to provide a stationary intake of the individual electrolytes, the patients were maintained on a rigidly constant metabolic regime. The diet in each case was determined by usual food habits and then identical weighed portions of each article of food were eaten daily. A constant fluid intake was maintained at a liberal level. After a week on the constant diet, consecutive 24-hour collections of urine were begun and continued throughout the period of study which was divided into a foreperiod of 6 to 8 days, a period during which the patient received sulfanilamide every 4 hours, followed by an afterperiod of about one week.

Two patients were submitted to this plan of study. Subject W. P. was a 26-year-old gardener well in all respects except for gonorrheal arthritis of the right knee of 4 months' duration. The joint became entirely well during treatment. The period of sulfanilamide administration, during which he received 1.33 grams of the drug every 4 hours, extended over 28 days. Subject E. C. was given 60 grams of sulfanilamide over a period of 10 days.

Analytical methods

The 24-hour collections of urine were preserved with toluol. A small portion of each voiding was collected under oil for measurement of pH which was done

[1] This is publication Number 45 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School.

[2] The expenses of this investigation were defrayed by a grant from the Commonwealth Fund.

colorimetrically by the method of Hastings, Sendroy and Robson (7). Immediately on completion of each 24-hour urine collection, the measurement of ammonia was carried out by the method of Folin as modified by Van Slyke and Cullen (8). The other analytical methods used were as follows: sodium, Butler and Tuthill (9); potassium, Fiske and Litarczek (10); total base, Fiske (11); calcium, Fiske and Logan (12); chloride, Eisenman (13); phosphorus, Fiske and Subbarow (14); sulfanilamide, Marshall (15); total nitrogen, the Kjeldahl method. The blood was collected under oil and the serum separated anaerobically as soon as clotting permitted. The CO_2 content of the serum was determined by the method of Van Slyke and Neill (16). Serum pH was measured colorimetrically by the method of Hastings and Sendroy (17). In obtaining measurements of other components of serum, the methods already cited were used.

Results

The measurements obtained from W. P. over the 42 days of study are displayed graphically in Figure 1. Several features of the data which describe the excretion of Na, Cl, K and NH_4 in the urine are readily apparent. The most prominent one is a very large rise in the excretion of sodium during the first day of administration of sulfanilamide. Over the remainder of the prolonged period of study the daily excretion of Na, although quite widely fluctuant, approximates the roughly defined foreperiod level. Immediately following the cessation of sulfanilamide administration, a progressive and extensive reduction of Na

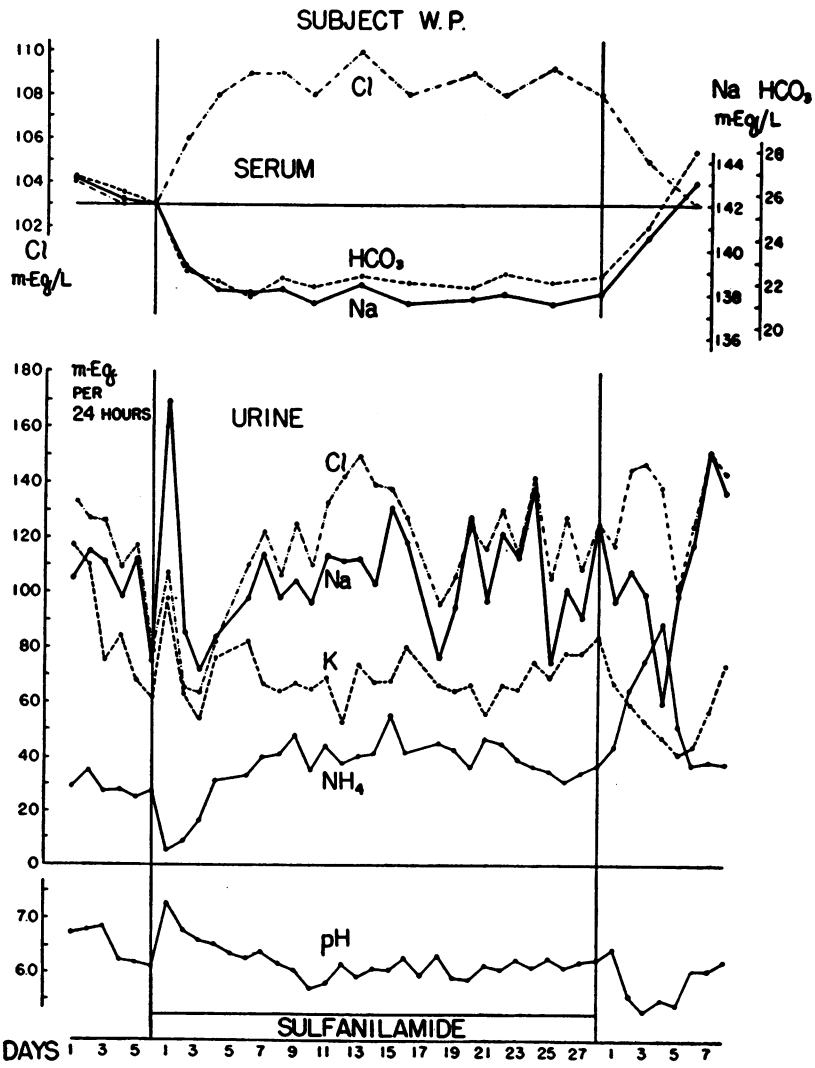

FIG. 1. DATA OBTAINED DURING A 28-DAY PERIOD OF SULFANILAMIDE ADMINISTRATION

excretion occurs over a 4-day period, which is then followed by a stepwise return to the region of the foreperiod level. The initial rise in Na is accompanied to only a slight extent by Cl, nor does Cl excretion in the afterperiod follow the large reduction in the excretion of Na. Thus, during the first day of sulfanilamide administration there is removal of Na in large excess over Cl and in the afterperiod the reverse event, a much more extensive removal of Cl than of Na. The measurements of K describe changes in excretion level in the same directions as Na but of considerably less extent. The NH_4 values show at the outset of the sulfanilamide period a brief but extensive recession and in the afterperiod a large rise; in other words, an inverse relationship to the two large components of fixed base excretion, Na and K. As would be expected, urine pH displays changes reciprocal with respect to NH_4.

The measurements of concentration of Na, HCO_3, and Cl in the blood serum are plotted in the upper section of the chart with reference to the values found on the day preceding the period of sulfanilamide administration and they clearly describe two events. At the outset of the sulfanilamide period the (Na) falls rapidly and at

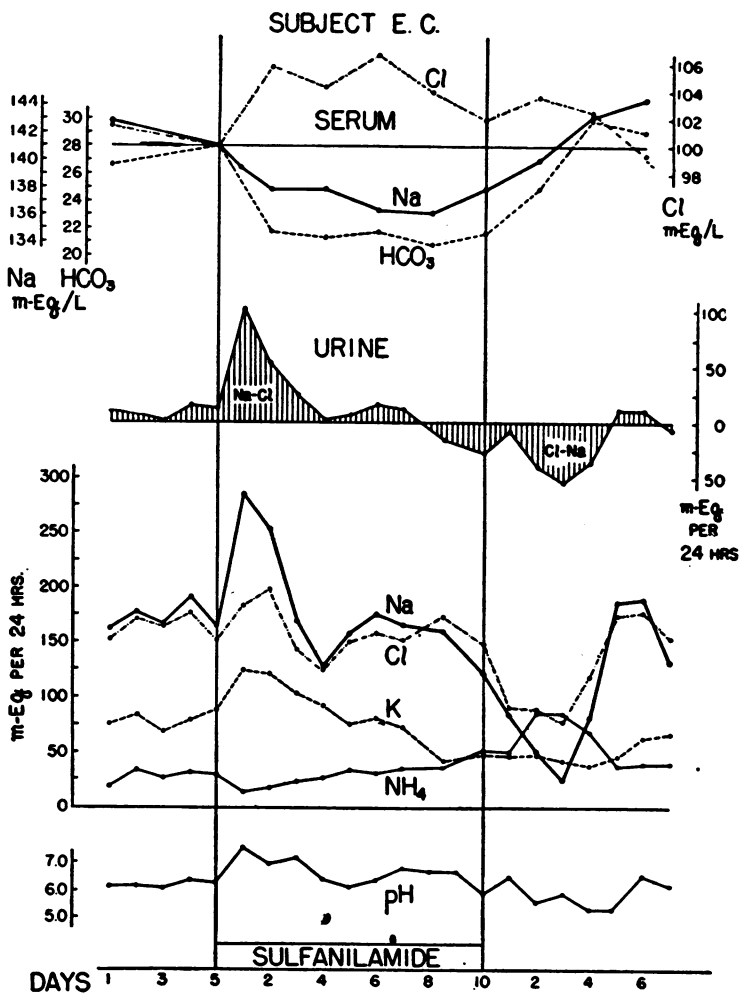

FIG. 2. DATA OBTAINED DURING A 10-DAY PERIOD OF SULFANILAMIDE ADMINISTRATION

In the middle curve the shaded area above the base line indicates the difference of sodium excretion-chloride excretion, while that below indicates chloride excretion-sodium excretion, demonstrating the lack of companionship between these two ions.

the end of the third day is about 4 m. eq. per liter below the initial value. This level is then approximately sustained until sulfanilamide is removed, whereupon (Na) returns in the course of 6 days to a usual value. These changes in (Na) are accompanied by closely equivalent changes in (HCO_3). The other event is a somewhat larger change of (Cl) in the other direction, producing an increase of about 6 m. eq. Here again there is the feature of rapid approach to the new level which is then held fairly steadily over the sulfanilamide period.

The data from the other subject, E. C., are recorded in Figure 2 and also in Table I. As may be seen in Figure 2, the features of change in the daily excretion values for Na, Cl, K, and NH_4 and in the concentrations of Na, HCO_3 and Cl found in the serum of W. P. are again described. The relationship of Na and Cl excretion is, however, much more clearly defined by the measurements obtained from this subject. To make quite clear the extent of disruption of the companionship of Na and Cl, the values for the initial excess of removal of Na over Cl and the subsequent larger excretion of Cl than of Na are plotted on the chart.

Discussion

If it be assumed that the extrarenal removal of Na, K and Cl by way of the skin and in the feces is a small fraction of the total excretion and has a fairly constant value, fluctuations in the daily quantity in urine, in the presence of a stationary intake, may be taken as measuring gain or loss from the body.

This premise is used with the reservation that the measurements of gain or loss of Na or Cl which it provides must be regarded as rather rough approximations. The daily excretion values for these extracellular electrolytes have

TABLE I

E. C.—Urine data

Date	Volume	Total base	Sodium	Potassium	Calcium	Average pH	Phosphorus	Chloride	Ammonia	Sulfanilamide	Total N
		total m.Eq.	*total m.Eq.*	*total m.Eq.*	*total m.Eq.*		*total m.Eq.**	*total m.Eq.*	*total m.Eq.*	*total grams*	*grams*
March 18.....	2540	258.5	162.1	75.3	11.1	6.15	40.7	151.9	23.57		12.193
March 19.....	2795	270.9	178.4	82.59	10.5	6.18	29.71	171.2	34.0		11.698
March 20.....	2198	261.7	166.2	69.3	9.9	6.10	32.1	165.9	25.9		10.427
March 21.....	2385	274.0	191.5	84.5	9.5	6.40	40.1	176.0	30.64		11.350
March 22.....	2105	254.2	164.6	87.6	8.9	6.30	43.2	151.7	29.09		11.311
SULFANILAMIDE 6.0 GRAMS DAILY BEGUN											
March 23.....	3000	415.6	284.3	123.53	11.1	7.50	63.7	183.7	12.84	1.436	12.387
March 24.....	2965	380.8	251.6	121.0	11.4	6.95	50.9	198.5	17.35	3.882	12.420
March 25.....	2780	277.9	169.2	103.6	12.8	7.17	54.4	143.14	22.6	4.099	12.638
March 26.....	2330	224.1	127.8	91.71	12.8	6.40	34.3	124.1	26.9	4.093	11.943
March 27.....	2540	249.8	157.6	76.1	12.7	6.17	30.6	150.2	34.2	4.461	13.270
March 28.....	2540	263.7	176.3	81.6	14.5	6.40	33.2	159.3	31.1	4.258	12.031
March 29.....	2180	244.1	165.7	72.8	14.6	6.82	45.2	152.6	36.3	4.349	13.024
March 30.....	2430	298.9	216.76	62.4	16.6	6.73	34.3	211.9	46.14	5.167	12.954
March 31.....	1830	158.7	102.9	22.4	11.8	6.72	29.2	135.7	28.6	4.392	11.722
April 1.....	2720	221.5	122.2	48.9	13.4	5.92	25.6	148.8	52.06	5.195	12.385
SULFANILAMIDE STOPPED											
April 2.....	1985	158.8	113.0	48.0	10.8	6.55	37.7	91.08	47.64	3.819	12.491
April 3.....	1545	106.6	50.91	51.8	10.4	5.60	37.8	90.64	85.7	1.328	14.080
April 4.....	1545	83.7	24.3	43.2	7.9	5.92	35.1	78.25	84.5	0.315	12.690
April 5.....	1550	140.6	81.7	39.5	8.5	5.32	40.0	118.0	68.8	0.084	10.856
April 6.....	2075	246.7	187.4	46.6	8.3	5.32	29.8	175.2	38.4	trace	9.844
April 7.....	2460	255.1	189.0	63.8	9.4	6.55	26.3	177.3	38.9	0	9.732
April 8.....	2420	255.3	145.6	65.8	8.3	6.22	45.5	152.6	39.94	0	8.906

* These values were calculated from the total phosphorus in mols from the pH by the use of the equation:

$$pH = 6.66 + \log \frac{HPO_4^=}{\text{Total P} - HPO_4^=}.$$

been found to oscillate considerably even when intake is accurately constant (18). However, in the presence of wide change in excretion, estimation of gain or loss obtained from an approximately defined foreperiod level may be accepted as dependably descriptive. On this basis the most conspicuous finding from the urine data is a large loss of Na at the outset of the sulfanilamide period which is to only a slight extent accompanied by an increase in chloride excretion. Along with this event the serum data describe a reduction of (Na) and an increase of (Cl). Rough calculation of the relationship of Na loss to (Na) reduction in the serum produces the information that the loss is much larger than the fall in concentration in the serum describes. Using the data from E. C. (Table I), and taking the average of the measurements of Na over the foreperiod as representing the level of excretion in urine which sustains Na balance in the body, a loss of 190 m. eq. is found over the first 2 days of sulfanilamide administration. Reduction of (Na) in the serum was 3.3 m. eq. per liter. Total extracellular fluid, on assumption that it amounts to about 20 per cent of body weight, was 12 liters for this subject. Thus a loss of 40 m. eq. of Na would account for the fall in plasma (Na). On the premise that Na is held in the body only in extracellular fluid, the remainder of the Na loss in urine, 150 m. eq., must be accompanied by an equivalent withdrawal of extracellular water. Since the water loss is presumably at the expense of interstitial fluid water in which the normal value for (Na) may be taken as 147 m. eq. per liter, the estimated reduction of extracellular fluid volume in this subject amounts to about one liter. Incidentally, this provides explanation of the rise of (Cl) found in the blood serum. The expected rise may be roughly estimated. The value for (Cl) in the serum at the beginning of the sulfanilamide period was 100 m. eq. per liter so that the 12 liters of extracellular fluid contained 1200 m. eq. of Cl. Excretion of Cl in the urine, above the foreperiod level, was 55 m. eq. over the first 2 days. The increased (Cl) caused by reduction of extracellular fluid volume to 11 liters should therefore be $1200 - 55/11 = 104$ m. eq. per liter, which is in the neighborhood of the value found, 105.8 m. eq. per liter. This objective explanation of the process of increase in plasma (Cl) does not, of course, tell us why renal control permits it.

Another clearly evident finding is an increased removal of potassium. Estimated from the foreperiod level of excretion, this loss of K for the first 2 days of the sulfanilamide period is 85 m. eq. The measurements of (K) in the serum show no appreciable change. Loss of one liter of extracellular fluid would remove only about 4 m. eq. of K. The increased excretion must therefore be derived from intracellular fluid where K is the largest component of the total base value. The observed reduction of (Na) in extracellular fluid of 3.3 m. eq. per liter may reasonably be supposed to make necessary a corresponding reduction of (K) in the adjacent fluid. If the intracellular fluid volume for this subject be taken as 30 liters (50 per cent of body weight), then the expected removal of K would be $30 \times 3.3 = 99$ m. eq. The loss of K therefore probably does not involve a reduction of intracellular fluid volume.

From the plasma data recorded in Figures 1 and 2, it may be seen that the changes in (HCO_3) and (Cl) are roughly reciprocal. Taken by themselves they would suggest very strongly that the bicarbonate reduction caused by the administration of sulfanilamide could be described as a "chloride acidosis". The close correspondence of the reductions of (Na) and of (HCO_3) makes it clear, however, that bicarbonate is lowered by removal of $BHCO_3$ and not by a process of displacement of the anion HCO_3 by Cl. The increase in (Cl) is therefore entirely gratuitous as an explanation of bicarbonate reduction and is also mysterious as regards its accommodation in the acid-base framework of the serum. As shown by the total base measurements in Table I, and also those of K and Ca, there is no replacement of the Na reduction by extension of the other components of serum base. As regards sulfanilamide itself, if it be assumed that this substance behaves as base and crediting it with divalency, the concentration measured in the serum would not cover more than a small fraction of the (Cl) increase. Among the anion components protein is the only one large enough to provide place by recession for the approximately 5 m. eq. per liter increase of (Cl). Since there is no reduction of the concentration of protein, base could be supplied only by alteration of its usual base equivalence value in

some way related to the presence of sulfanilamide. That such an event occurs is the only surmise that the authors are able to devise from the data at hand. The manner of the covering of the (Cl) increment therefore awaits further investigation.

The changes in acid-base excretion in urine and the accompanying changes in the electrolyte structure of the plasma which these data describe suggest at first glance a disability of renal control in the presence of sulfanilamide. This surmise, however, is not altogether suited by the outstanding feature of these findings; namely, an initial large removal of sodium which is then followed by a steadily sustained excretion at the foreperiod level. The alternative explanation that the changes in the electrolyte structure of the serum represent adjustments which are made necessary by the presence of sulfanilamide and which are thereafter accurately sustained by the kidney at least deserves consideration, the authors believe, in spite of the implied offense to the threshold conception of renal control. The curious inverse change in the serum levels for (Na) and (Cl) is not to their minds readily referable to an error in tubular function. The authors, however, admit that these reflections scarcely constitute an argument. It is perhaps worth noting that these effects from sulfanilamide administration bear a resemblance in some respects to those found by Gamble, Blackfan and Hamilton (19) for the so-called acid-producing salts. There is the same removal of Na and K with an accompanying loss of body water and the same large increase in serum (Cl). They record the curious finding that this increase in (Cl) is apparently not a direct consequence of the ingestion of calcium chloride or of ammonium chloride since it also occurs to the same extent following the administration of ammonium sulfate. There is no appreciable change in plasma fixed base so that, in the case of these salts, the reduction of plasma HCO_3 which occurs is clearly referable to the increase in (Cl).

THE RELATIONSHIP OF HYPERPNEA AND BICARBONATE REMOVAL IN URINE FOLLOWING INGESTION OF SULFANILAMIDE

The finding, following sulfanilamide administration, of a removal of Na in excess over Cl in the urine, reduction of serum bicarbonate and increased pulmonary ventilation produces the entertaining question of the causal relationship of these events. Does the sequence of these changes begin with the alteration of breathing or with the removal of fixed base? The usual rôle of hyperpnea as an adjustment of carbonic acid in the plasma in the presence of bicarbonate reduction points to the base loss in the urine as the initial event. Overbreathing experiments, however, have shown that primary reduction of carbonic acid in the plasma is followed by a removal of bicarbonate in the urine, and Hartmann's hypothesis is that the first step in sulfanilamide effect is hyperpnea produced presumably by action of the drug on the respiratory center. The essential item of Hartmann's evidence consists in demonstration of an increase in plasma pH, indicating a primary alkalosis for which bicarbonate reduction by removal in urine may be regarded as compensatory. The change in pH which Hartmann reports is not, however, in most instances of a convincing magnitude. Here it may be pointed out that since pH is in process of adjustment, whether by removal of bicarbonate in urine or by increased ventilation of the lungs, large departures from its normal value would not be expected. It would therefore seem desirable to measure other factors in the situation which should exhibit a greater width of change than the closely guarded pH value. Moreover, the question of the sequential relationship of the alteration in breathing, the reduction of plasma bicarbonate, and the removal of fixed base in the urine is obviously answerable if the position in time of these events following the administration of sulfanilamide can be clearly defined. To this end observations were obtained from two subjects.

Plan of experiments

The subjects were healthy young male adults. The respiratory data obtained were the rate of lung ventilation, O_2 consumption, CO_2 production and alveolar CO_2 tension.[3] In arterial serum, pH and CO_2 content were measured, and CO_2 tension was calculated. In the urine, pH and the rate of removal of bicarbonate were determined. These

[3] We are indebted to Dr. John H. Talbott for these determinations.

data were obtained directly before and at several 1 to 2-hour intervals after administration of a single large dose of sulfanilamide. The spirometer collections were over 50-minute periods just preceding the taking of serum samples. In addition to the two sulfanilamide experiments, a third set of observations was obtained from one of the subjects at the beginning and at the end of a 50-minute period of voluntary overbreathing.

Results and discussion

The data from these experiments are recorded in Table III and are also shown graphically in Figure 3. The results of the two sulfanilamide experiments are in good agreement. The rise in serum pH described by Hartmann was not found in these two subjects. Actually, in this early stage of sulfanilamide effect, a fall of pH was observed, but of such slight extent that its significance is doubtful. The measurements of urine bicarbonate show a nearly constant rate of removal which, moreover, has about the same value for both subjects. Since the rate found from urine collected over the first period following sulfanilamide administration (recorded on the chart

TABLE II

E. C.—*Serum data*

Date	Total base	Sodium	Potassium	Calcium	Phosphorus*	Chloride	Carbon dioxide	Sulfanilamide
	m.eq. per liter	*m.eq. per liter*	*m.eq. per liter*	*m.eq. per liter*	*m.eq. per liter*	*m.eq. per liter*	*total m.M.*	*mgm. per 100 cc.*
March 18	152.2	142.8	3.795	4.6	2.32	101.8	29.3	0
March 22	150.7	141.2	4.113	4.87	2.39	99.8	28.2	0
SULFANILAMIDE BEGUN								
March 23		139.5						3.45
March 24	148.8	137.9	4.18	4.68	2.37	105.8	21.8	4.38
March 26	148.5	138.0	4.41	4.56	2.22	104.3	21.4	6.29
March 28	144.5	136.3	4.16	4.65	2.06	106.6	21.7	5.26
March 30	145.5	136.0	3.88	4.68	1.97	103.9	20.8	6.31
April 1...	147.8	138.0	4.12	4.68	2.15	102.0	21.6	5.90
APRIL 2—SULFANILAMIDE STOPPED								
April 3...	151.8	140.1	4.05	4.34	1.97	103.64	24.9	±
April 5...	155.0	143.2	4.40	4.57	1.90	102.36	29.9	0
April 7...	154.8	144.4	4.76	4.60	1.86	99.4	29.0	0

* Calculated for pH 7.4 by the equation:

$$7.4 = 6.6 + \log \frac{HPO_4^-}{\text{Total P} - HPO_4^-}.$$

TABLE III

Data obtained in experiments relating hyperpnea and bicarbonate removal in the urine

Time	Respiration					Serum (arterial)			Urine			
	Ventilation	CO_2	O_2	R.Q.	Alveolar CO_2	pH	pCO_2	HCO_3	Volume	pH	HCO_3	HCO_3
	liters per minute	*cc. per minute*	*cc. per minute*		*mm. Hg*		*mm. Hg*	*m.eq. per liter*	*cc.*		*total m.eq.*	*m.eq. per minute*
SULFANILAMIDE EXPERIMENT I E. J.												
7:35 a.m.....	7.80	245	280	0.87	40.6	7.41	41	26.9	50	6.6	1.58	0.032
10:25 a.m.....	6.84	220	273	0.81	39.3	7.38	39	23.8	200	7.8	33.41	0.197
12:30 p.m.....	7.80	229	293	0.78	35.6	7.38	35	21.3	420	8.0	24.20	0.194
3:45 p.m.....	9.26	238	318	0.74	36.4	7.40	35	22.4	120	8.1	26.50	0.135
13.3 grams sulfanilamide and 100 cc. H_2O at 9:55 a.m.												
SULFANILAMIDE EXPERIMENT II R. M.												
7:23 a.m.....	4.64	162	277	0.75	41.7	7.42	40.3	26.4	51	5.5	0.10	0.002
8:50 a.m.....	4.66	164	218	0.75	36.7	7.38	40.2	25.8	410	7.3	17.22	0.198
10:12 a.m.....	4.98	166	221	0.75	35.2				350	7.5	15.60	0.190
11:25 a.m.....	5.25	168	227	0.74	35.4				210	7.7	13.89	0.166
12:30 p.m.....	5.42	165	227	0.72	35.2	7.38	35.3	22.2	95	7.8	10.77	0.026
13.3 grams sulfanilamide and 200 cc. H_2O at 8:35 a.m.												
OVERBREATHING EXPERIMENT R. M.												
7:35 a.m.....	5.70	167	215	0.78	33.1	7.40	40.0	21.2	165	5.5	0.26	0.005
8:30 a.m.....	8.54	206	206	1.00	20.7	7.57	22.0	19.5	210	6.9	3.92	0.071
50-minute voluntary hyperventilation begun at 7.37 a.m.												

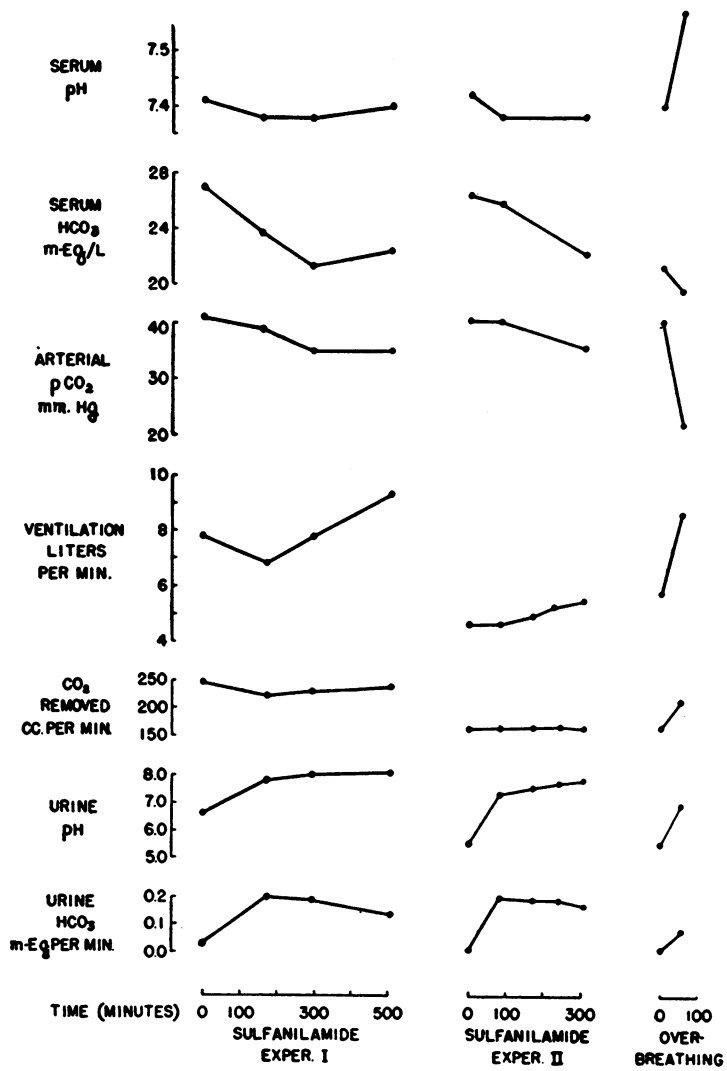

FIG. 3. DATA IN TABLE III DEMONSTRATING THE DIFFERENCE BETWEEN THE SULFANILAMIDE EXPERIMENTS AND THE OVERBREATHING EXPERIMENT

at the end of the period) has approximately the same value as in the subsequent periods, it is evident that establishment of this rate of removal is an almost immediate effect of sulfanilamide. The change in urine pH corresponds. Serum bicarbonate is found to decline over a period of 5 hours when, according to the longer experiment (I), it becomes roughly stationary. The measurements of the volume of lung ventilation have a critical significance. As may be seen in Figure 3, no increase in ventilation is found at the end of the first period following sulfanilamide. Gradual development of hyperpnea in these two subjects is described by the subsequent measurements. Since the urine data demonstrate that the process of bicarbonate removal is fully established during the first period following sulfanilamide, priority of this event would seem to be clearly indicated. This inference is supported by the measurements of arterial CO_2 tension. By the end of the first period pCO_2 in Experiment I has fallen only slightly and in Experiment II is found unchanged. A discordant item in the evidence must be admitted. The measurements of alveolar CO_2 tension show a definite reduction at the end of the first period in the second experiment and are

therefore in direct disagreement with the measurements of ventilation and of arterial pCO_2. The authors are unable to account for this discrepancy. A finding of incidental interest is that the rate of CO_2 removal by the lungs is not measurably increased by the gradual development of hyperpnea. Appreciable reduction referable to CO_2 removed in the urine as bicarbonate would not be expected since this quantity is relatively minute, amounting to about 6 cc. per minute.

The defects of resemblance of the data found following sulfanilamide administration to those data produced by the 50-minute overbreathing experiment, which describe a situation of primary alkalosis, are clearly evident in Figure 3. The measurements of serum pH and of arterial pCO_2 show that the expected change of these values in the presence of increased ventilation of the lungs is rapid and extensive and the urine data demonstrate that adjustment by removal of bicarbonate is under way by the end of the 50-minute period. Here, however, it may be noted that in the presence of great change in ventilation the rate of removal of bicarbonate is much smaller than is found in the sulfanilamide experiments in the absence of appreciable change in ventilation. This fact suits the secondary position of bicarbonate removal in the overbreathing experiment and points clearly to its primary significance following sulfanilamide.

The total evidence of the data from these experiments thus quite definitely indicates that the hyperpnea which develops following sulfanilamide administration should be regarded as an adjustment to an initial removal of fixed base in the urine.

SUMMARY

Over a period of continued administration of sulfanilamide, several alterations of acid-base metabolism are found to occur. There is a large loss of sodium accompanied by a smaller loss of potassium and little or no loss of chloride ion. The concentration of sodium in blood plasma is reduced to the extent of 4 to 5 m. eq. per liter. There is no replacement of this deficit by extension of the other components of total base. The loss of sodium is much larger than the reduction of its serum concentration indicates and therefore presumably involves a considerable withdrawal of extracellular water. The quantity of potassium lost suits the hypothesis of a reduction of total base concentration in intracellular fluid to the extent caused in extracellular fluid by the recession of sodium. The fall of sodium concentration in the plasma corresponds closely with and explains a reduction of bicarbonate. The concentration of chloride ion, on the other hand, is increased to the extent of 5 to 6 m. eq. per liter above the initial value. This elevation agrees in extent with a reduction of extracellular fluid volume estimated from the sodium loss. The accommodation, in terms of base equivalence, of this extension of chloride ion in the presence of an actual reduction of total base is unexplained. An outstanding feature of these alterations of acid-base excretion and of the electrolyte structure of the plasma is that they occur rapidly (within 1 to 3 days) at the outset of the period of sulfanilamide administration. Electrolyte exchange and the altered values in the plasma are then steadily sustained until sulfanilamide is removed. The initial losses of sodium and potassium are then rapidly recovered and the normal electrolyte pattern of the plasma is restored.

Observations of respiratory change, serum alterations and the removal of sodium in the urine at short (1 to 2-hour) intervals following ingestion of a single large dose of sulfanilamide clearly describe the entrance of bicarbonate into the urine as an almost immediate event which is followed by a gradual development of increase in lung ventilation. The hyperpnea observed during sulfanilamide therapy may therefore be regarded as a secondary event compensatory to plasma bicarbonate reduction caused by removal of fixed base in the urine.

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