THE EFFECT OF ACID AND BASE INGESTION UPON THE ACID-BASE BALANCE.*

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Previous to the conception of hydrogen ion concentration as an index of acidity or alkalinity, only hazy notions existed as to the reaction of the body fluids. Soon after the acid-base balance was more fully comprehended, it became a prevalent idea that the reaction of the blood and tissues was maintained within exceedingly close limits and that any appreciable variation would be incompatible with life. Haldane (1) in 1922, speaking of the pH of the blood, wrote:

"Hasselbalch estimates that a difference of .03 can be detected in single determinations by the electrometric method; but this is a very large difference, corresponding to an increase of 250 per cent in the breathing. Time and effort will continue to be wasted on futile measurements until the extreme fineness of the physiological regulation of pH in the blood and tissues is more fully realized."

He further states: "A continued difference of 0.1 in pH would in all probability cause danger to life. This is a much lower limit than has commonly been assumed."

These conclusions were based on many careful observations but direct pH determinations were few. For example, Davies, Haldane, and Kennaway (2) studied the effect of the ingestion of 500 cc. of 0.116 N HCl taken within 80 minutes but noticed no fall in the alveolar CO₂ tension. Similarly, 30 gm. of NaH₂PO₄·H₂O caused no fall. However, Hasselbalch (3) as early as 1912 demonstrated that a meat diet increased the relative acidity of the blood over that of a vegetable diet by as much as 0.02 pH.

* This paper is one of a series of studies on metabolism from the Harvard Medical School and allied hospitals, a part of the expense of which has been paid by the Proctor Fund for the study of chronic diseases.
More recently Haldane (4) conducted an experiment where
NH₄Cl was ingested, 20 gm. the first 2 days and 15 gm. the 3rd.
The CO₂ capacity of the blood at 40 mm. Hg dropped from 48.1
before, to 28.2 volumes per cent at the end of the 3rd day, with
a similar drop in the alveolar CO₂ tension from 38.8 to 27.8 mm.
Hg. He figured that 96 per cent of the acidosis was compensated
by increased respiration. Similarly, Haldane, Hill, and Luck
(5) showed that 85 gm. of CaCl₂ taken over a period of 3 days
caused a markedly acid urine with increased NH₃ output and a
drop in the alveolar CO₂ tension.

It was my fortune to have under observation a group of patients
suffering from chronic lead poisoning, who were being treated by
Dr. J. C. Aub for long periods with large doses of acids or alkalies,
or acid- or alkali-producing substances for the purpose of increas-
ing the elimination of lead. Aub and his coworkers (6) have
shown that lead is deposited in the skeleton largely as a calcium
lead phosphate and that its minimal solubility is approximately
at the normal pH of the blood with increasing solubility in either
direction of the pH range. During the medication of these pa-
tients the acid-base balance of the blood was carefully studied.

Methods.

The patients in all of these experiments were on a rest schedule
which consisted of lying in bed or sitting in a chair. Occasionally
short walks up or down the ward or hall were permitted. Ascend-
ing and descending a stairway leading from the ward was used as
an exercise test.

The diets were constant throughout the experiments and con-
trol periods and consisted of protein, 1.25 gm. per kilo, carbohy-
dratre 1200 to 1800 calories, and fat 300 to 600 calories in 24 hours.
The diet consisted largely of potatoes, bread, butter, sugar, meat,
and fruit. The last consisted of 100 gm. each of apples and
bananas per day. The Ca intake was low, approximately 100
mg. per day unless separately added to the diet as indicated under
medication. Fluid intake was limited to approximately 3500 to
4000 cc.

The various acids, alkalies, or salts were given in water in rather
dilute solutions from 8.00 a.m. to 6.00 p.m. distributed over 2
hour intervals.
Unless otherwise specified, the blood samples were taken at about 5.00 p.m. Venous blood and in one case arterial was taken from the arm directly under paraffin oil over powdered oxalate. The blood was chilled immediately in ice water and the determinations were done within 30 minutes. The pH and CO₂ determinations were done directly on the whole blood, as described in previous papers by the writer (7). The CO₂ content was determined by the Van Slyke constant volume apparatus and the pH by means of the hydrogen electrode at 37.5°C. The hydrogen which was equilibrated with the blood contained 5.5 per cent CO₂. The CO₂ tension was calculated from the Henderson-Hasselbalch equation using 0.0587 as the solubility factor for CO₂ in blood and a pK value for whole blood of 6.15.

The respiratory volume per minute was determined by means of a rebreathing soda-lime spirometer of the Benedict-Collins recording type with chronograph attached.

EXPERIMENTAL.

Administration of Acids or Acid-Producing Substances.

The first series of observations was made upon P. M-n during a period of H₃PO₄ administration. This patient was a male, 48 years of age, Greek, and had been a rubber mixer for the 7 preceding years. The acute symptoms of severe abdominal colic and marked ease of fatigue had subsided but a bilateral wrist drop and a general muscular weakness were still present. At the time of observation the patient had been hospitalized for 2 months and the hemoglobin and red blood cell count had increased from 75 to 85 per cent and 3,700,000 to 4,500,000 respectively. During this time the non-protein nitrogen had decreased from 51 to 36 mg. per 100 cc. of blood and the phenolsulfonephthalein excretion averaged well over 50 per cent for 2 hour periods.

The variations in venous blood pH, total CO₂ and pCO₂ together with volume respiration are also shown graphically in Fig. 1. The amount of H₃PO₄ that could be tolerated by mouth was approximately 17 gm. per day so from the 11th day of medication on, an additional amount of (NH₄)₂HPO₄ was given to see whether this would act similarly to NH₄Cl and produce a further drop in pH. However, such an action was not noticed to any
marked degree with the addition of 4 to 8 gm. of \((\text{NH}_4)_{2}\text{HPO}_4\). From approximately the 14th day to the 25th day, the acidosis remained at about a level with a pH of approximately 7.20 and a total CO\(_2\) content of 28 volumes per cent. The minute volume respiration increased from 6 before acid ingestion to approximately 10 liters during the acidosis, while the venous pCO\(_2\) dropped from about 44 to 38 mm. Hg. On the 22nd day an arterial blood sample was obtained and the pH was 0.02 higher and the total CO\(_2\) and pCO\(_2\) less in about the normal ratio. Weakness, headaches, and loss of appetite were noted during the course of the medication but in general the condition of the patient was quite good while at rest. When any exertion was attempted, however, marked distress resulted. The recovery from the acidosis was rapid and complete.

Fig. 2 shows the results of H\(_3\)PO\(_4\) medication upon this same patient 2 months later. The results were very similar except that as much acid was not given and the pH and total CO\(_2\) did not drop as far. From the 10th day on, calcium lactate was also given orally but not simultaneously with the acid. This was done to ascertain the effect of a positive Ca balance upon the lead excre-
The effect of the calcium lactate was nearly a complete neutralization of the acidosis, undoubtedly due to the formation and excretion of calcium phosphate. During this period of acidosis as well as the previous one, there was a definite loss in weight.
of about 8 per cent of the total. The greater part of this occurred the first 4 or 5 days and was undoubtedly due to dehydration as there usually was a definite polyuria and purgation during this time but not later.

A similar phosphoric acid acidosis was obtained in the case of J. T-a. This patient was a male, 34 years of age, Lithuanian and had been a rubber mixer for the 5 preceding years. The acute symptoms of lead poisoning had subsided a month before this period of acid medication but a bilateral wrist drop of moderate grade with some weakness of the muscles of the upper arms and shoulder girdle remained. The hemoglobin was 75 per cent and the red cell count 3,900,000 with marked stippling of cells. The renal function and blood non-protein nitrogen were normal. The results of this experiment are shown in Fig. 3. The findings were very similar to those obtained in the case of P. M-n. Inasmuch as the blood samples were usually taken toward the end of the day of medication and no acid was given during the night, in this case on the 11th day a blood sample was obtained in the morning before any acid was given. These results, compared with those obtained after about four-fifths of the acid was given, show that there is quite a marked diminution of the acidosis overnight.
Experiment 4, Fig. 4, shows the results of $H_3PO_4$ and $(NH_4)_2HPO_4$ ingestion for a period of 10 days in the case of J. L-r. This patient was a male, 32 years of age, Austrian, and his occupation was that of a chauffeur. His complaint had been severe generalized abdominal cramps. Examinations showed a pale individual with a marked alveolar lead line. There was no muscle weakness. The red blood cell count was 3,600,000 and hemoglobin 65 per cent at time of admission but there was an increase up to 4,000,000 and 75 per cent respectively 3 weeks later at the time of study. There was no evidence of any renal insufficiency. An average of approximately 15 gm. of $H_3PO_4$ and 4 to 7 gm. of $(NH_4)_2HPO_4$ daily for 9 days produced an acidosis below pH 7.20. At the end of this period the patient noticed considerable lassitude, headaches, muscle pains, and marked respiratory distress upon exertion. There was practically a complete return to normal 24 hours after the acid was stopped.

Experiment 5, Fig. 4, shows in the case of J. T-a (2 weeks after the experiment shown in Fig. 3) the effect of daily doses of 6 to 14 gm. of $(NH_4)_2HPO_4$. Only a very moderate acidosis resulted and there was no particular symptomatic upset beyond slight purgation the first few days and moderate lassitude toward the close of the 10 day period.
Fig. 5 also shows the results of (NH₄)₂HPO₄ ingestion in the case of J. S.-w. This patient was a Negro, male, 30 years of age. He recently had mild abdominal colic and nausea. Examination revealed a well built, strong individual with a definite alveolar lead line. This patient had had a posterior gastroenterostomy a year previously for a bleeding gastric ulcer. At the time of the present admission all evidence suggested that the ulcer was healed. The hemoglobin was 78 per cent and the blood red cell count 3,900,000. There was no evidence that showed any renal insufficiency. During the first 11 days of (NH₄)₂HPO₄ ingestion there was only a slight shift in the reaction of the blood in the direction of an acidosis. During the 6th and 8th days there was a slight shift toward the alkaline side, the cause of which remained unexplained. During this period there was no symptomatic change. On the 12th day of the experiment, 10 gm. of NH₄Cl were substituted for the phosphate. Very shortly the total CO₂ dropped together with the pH and the respiratory minute volume increased to 10 liters per minute. Lassitude, headaches, and loss of appetite developed and the acid feeding was discontinued on the 20th day with a quick return to normal.

The effect of prolonged administration of NH₄Cl is shown in
Experiment 7, Fig. 6. An average of approximately 12 gm. was given daily for 17 days. There was a rapid drop in the blood pH and total CO₂ for the first 6 days and then there was a gradual decrease until the end of the 16th day. In this case an acidosis in the vicinity of pH 7.20 was maintained for about 9 days with a minimal value of pH 7.17. During the period of NH₄Cl feeding the respiratory volume increased from 7.80 to 15.05 liters per minute. This patient noticed considerable lassitude and moderate headaches during the last 12 days of the experiment. He desired to remain in bed continuously and at times appeared quite listless. During the last few days he complained of considerable epigastric distress with occasional abdominal cramps. The recovery following this period of acidosis was not quite as rapid as usual, for even 48 hours after the NH₄Cl was stopped, moderate lassitude and weakness persisted.

Experiment 8, Fig. 7, shows a similar response to NH₄Cl ingestion in the case of P.M-n. In this case the daily amount of NH₄Cl averaged about 8 gm. per day for 14 days. Diuresis and thirst were fairly marked during the first few days of the experiment but disappeared later. The recovery, particularly as to lassitude and
weakness, was not quite complete at the end of the 2nd day but a normal state had practically been reached by the end of the 3rd day.

The effect of NH₄Cl upon P. M-n as recorded in the last experiment was again observed 2 weeks later under similar conditions and is shown in Experiment 9, Fig. 8. This time the patient tolerated only about 10 gm. of NH₄Cl daily and even then he developed headache, backache, and loss of appetite during the 3rd day. This distress continued with crampy pains in muscles of arms and legs even though the NH₄Cl was reduced to 7 gm.

daily. On the 6th day the urine showed a moderate amount of albumin, a few red blood cells, and granular casts. The blood non-protein nitrogen was 68 mg. per 100 cc. No NH₄Cl was given during the 6th and 7th days. On the 7th day the non-protein nitrogen was 58 and on the 8th, 42 mg. per 100 cc., and the urine showed only an occasional granular cast. The blood pH at the end of the 6th day was still 7.28 and the total CO₂ 29.5 volumes per cent even though no NH₄Cl was given that day. The patient felt so well on the 8th day that NH₄Cl was again started in small amounts. There was no marked symptomatic disturbance, and the urine remained negative and the blood
non-protein nitrogen normal. The NH₄Cl was discontinued on the 19th day with a blood pH of 7.20 and a total CO₂ of 28.2 volumes per cent.

The effect of CaCl₂ is shown in Experiments 10 and 11, Fig. 9. The subjects were two apparently normal young men and the usual daily hospital work was continued during the experiment. A constant diet was maintained and fluids were limited to 2400 cc. daily. 15 gm. of CaCl₂ were given daily, 5 gm. after each meal. At the end of the 8th day the discomfort became so great that work could no longer be continued and the CaCl₂ ingestion was stopped.

The distress consisted of ease of fatigue even upon slight exertion, general mental and physical lassitude and, in the case of H. S-1 moderate headaches. During the first 2 to 3 days there was a definite diuresis but after this the urine output soon returned to normal.

**Administration of Alkali or Alkali-Producing Substances.**

The effect of NaHCO₃ in the case of J. S-w is shown in Experiment 12, Fig. 10. At first 12 and later 20 gm. of NaHCO₃ were given daily for 16 days. The blood total CO₂ and pH increased in such a ratio that the pCO₂ remained practically the same or
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only slightly increased. The volume respiration increased slightly. During the course of the period the patient developed lassitude and lethargy, nausea, occasional headaches, and later general malaise with loss of appetite. Exercise consisting of ascending and descending a short flight of stairs produced marked fatigue, dizziness, nausea, and headache. The patient responded very poorly to partial anoxemia as compared to a similar test during the control period. A rebreathing spirometer of 18 liters capacity was used for this test and the patient became distressed at 11 per cent $O_2$, while formerly he could easily reach a much lower level. In spite of the malaise and poor appetite, there was a gradual gain in weight of about 1.4 kilos.

The effect of large doses of NaHCO$_3$ in the case of J. T-a is shown in Experiment 13, Fig. 11. Approximately 40 gm. of NaHCO$_3$ were given daily for 21 days. The symptomatic response was very similar to that in the preceding experiment although twice the daily dose was given. There was only a moderate increase of 0.2 to 0.3 pH of the blood in the latter case in which the high alkali dosage was given. The response to exercise and partial anoxemia was also very poor in this case. The urine did not show albumin, casts, or cells at any time. After the alkali was stopped, the lassitude persisted for about 2 days.
The effect of approximately 40 gm. NaHCO₃ a day, in the case of P. M-n, is shown in Experiment 14, Fig. 12. The response of blood pH and total CO₂ is quite similar to that in the preceding experiment. After the pH reaches a value of approximately 7.55, a level is maintained in that vicinity. In this case there was
practically no change in pCO₂ but the volume respiration was definitely increased. At one time the patient showed a slight trace of albumin, granular casts, and a few epithelial cells and leucocytes but these disappeared in a few days without stopping the alkali. The patient complained of lassitude, drowsiness, and was quite listless and disinclined toward all activity after the first few days of alkali ingestion.

The effect of Na citrate in a dosage similar to that of NaHCO₃ in the preceding experiments is shown in Experiment 15, Fig. 13. The subject, J. M-r, was a male Negro, approximately 35 years of age. He had been under observation for about a week for the complaint of weakness and mild abdominal colic. There was no evidence of renal insufficiency. The hemoglobin was 80 per cent and the blood red cell count was 4,100,000. The response to Na citrate was quite comparable in all respects to that of NaHCO₃. The blood pH had increased to 7.53 and the total CO₂ to 67 per cent. Lassitude and loss of appetite developed and the response to exercise and anoxemia was poor. Recovery from the blood changes and symptomatic distress was practically complete in 2 days.
DISCUSSION.

That the pH of the blood can readily be changed by several tenths in either direction from the normal and maintained for several weeks without disastrous effect is demonstrated. Experiments 1 to 10 show that the pH can be lowered quite rapidly in 4 to 6 days from values of 7.45-7.40 to 7.30-7.25. After this the drop becomes more gradual until the low values of 7.20 to 7.15 are reached in 10 to 20 days of acid ingestion. The longest period of acidosis maintained was in Experiment 1, Fig. 1, where it extended to 25 days of H₃PO₄ and later also (NH₄)₂HPO₄ ingestion. During the latter 9 days of the experiment the blood pH was maintained in the vicinity of 7.20. The most severe acidosis, pH 7.17, was obtained after 16 days of NH₄Cl ingestion as shown in Fig. 6. H₃PO₄, NH₄Cl, and CaCl₂ can be employed successfully to produce definite lowering of the blood pH. H₃PO₄ is quite unpleasant to take by mouth but it can be taken in amounts of 15 to 17 gm. daily. NH₄Cl is about twice as efficient for producing a grade of acidosis similar to that caused by an equal weight of H₃PO₄. 15 gm. of NH₄Cl can well be taken daily and will in approximately a week’s time produce a pH lowering to 7.20 as shown in Experiments 7 and 8.

The measurement of blood pH during ingestion of alkali or alkali-producing substances shows that a real blood alkalosis can be produced and maintained. NaHCO₃ ingestion in amounts of approximately 40 gm. daily produced a fairly rapid increase in blood pH from 7.40 to 7.44 to approximately 7.50 in 3 to 4 days, with a subsequent gradual rise to about 7.50 to 7.57 in 2 to 3 weeks (Experiments 12, 13, and 14). In Experiment 14, Fig. 12, the pH value remained at a level at 7.55 during the last week even though 40 gm. of NaHCO₃ were administered daily. At this level the acid-base relationship had established a new balance with excretion of base equalling the intake.

Na citrate in amounts equal to the Na equivalent in NaHCO₃ produces an effect on the blood pH practically equal to that of the latter as shown in Experiment 15.

*Total CO₂, CO₂ Tension, and Respiration.*

Haldane had previously shown that NH₄Cl taken in 15 to 20 gm. amounts for 3 days distinctly lowered the CO₂ capacity of the
blood. He demonstrated a fall in the CO₂ capacity from 48.1 to 28.2 volumes per cent with a simultaneous drop in the alveolar CO₂ from 38.8 to 27.8 mm. Hg. An increased volume respiration from 6 to 10.4 liters per minute was observed in this case and Haldane concluded that 96 per cent of the acidosis was compensated by the increased respiration. On the other hand, Davies, Haldane, and Kennaway found no drop in the alveolar CO₂ after the ingestion of 500 cc. of 0.116 N HCl or after 30 gm. of NaH₂PO₄·H₂O.

In all our apparently normal cases, acid or alkali ingestion caused a change in the total CO₂ content of the blood that closely paralleled the pH change. The ratio of pH to CO₂ content remained such that no gross changes occurred in the CO₂ tension. However, there was a distinct tendency of the CO₂ tension of the venous blood to fall in acid feeding but not to the magnitude that occurred in Haldane's arterial blood, judging from his alveolar CO₂.

In the one case where we obtained arterial blood during severe acidosis (Experiment 1, 22nd day), there was a more distinct fall in pCO₂, more comparable to that estimated from the increase in volume respiration. Not only is it natural for the changes in the venous pCO₂ to be retarded over that of the arterial tension, but venous blood with a lowered bicarbonate content must necessarily have an increased CO₂ pressure in order to carry away the CO₂ from the tissues at the normal rate, assuming a constant blood flow. Therefore, it is perfectly possible that during a simple acidosis the venous blood has a normal pCO₂ while that of the arterial blood is definitely decreased. Consequently, the CO₂ tension of the tissues is probably still higher than that of the venous blood and a more marked tissue acidosis exists than either arterial or venous blood pH indicates.

The respiratory minute volume increased in all cases of acid feeding and in general varied inversely with the pH of the venous blood. The ventilation increased from approximately 5 liters per minute to 10 liters and in the more severe acidosis, pH 7.20, increased to 15 liters per minute. Haldane states in respect to his case of NH₄Cl acidosis: "When the alveolar CO₂ fell, there was marked air-hunger. The increased frequency and depth of breathing was obvious. Thus at a time when the alveolar CO₂ was 29.7 mm. the volume breathed per minute when sitting in a chair was 10.4 liters."
Our experience in this respect has been that with the patients lying quietly in bed the volume respiration could easily be doubled without any obvious increase by inspection. None of our patients while at rest showed any tendency toward air-hunger even though the blood pH was below 7.20, but only slight exertion would produce a marked dyspnea. In the case of J. L-r, Experiment 4, with a blood pH of 7.19, walking slowly across the room and back, a total of 45 feet, caused a moderate hyperpnea of 27.6 liters per minute, while later with a pH of 7.40, this same amount caused the ventilation to increase to only 13.2 liters per minute.

During the course of induced alkalosis the change in the total CO₂ content of the venous blood paralleled that of the pH closely. Here too, as in the acidosis, the relationship remained such that the pCO₂ remained nearly constant. In two of the four cases of alkalosis, there was a slight rise in the pCO₂ for the 1st week. There seemed to be a slight increase in the volume respiration during the course of the alkalosis as previous workers have already observed (8). In the case of P. M-n, Experiment 14, the ventilation increased from 6 to approximately 8 liters per minute. The patients with alkalosis were all very sensitive to anoxemia. Ordinarily these subjects could easily lower the O₂ content of a rebreathing spirometer from 20.8 per cent to 5 or 6 per cent in 7 to 8 minutes without objective symptoms, but the patient with alkalosis became dizzy, developed headaches, had visual and auditory disturbances before 10 per cent O₂ was reached in the course of 4 to 5 minutes. In all probability, the patient in alkalosis is suffering from a mild anoxemia even at atmospheric O₂ pressure. It is quite possible that this anoxemia is responsible for the increased volume of respiration during alkalosis following alkali ingestion. Not only does the alkalosis increase the affinity of the hemoglobin for O₂ and thus diminish the supply to the tissues, but it probably depresses tissue oxidation also (9).

Symptomatology.

It is now nearly 50 years since Walter's observations that administrations of large doses of dilute hydrochloric acid to rabbits produced listlessness, air-hunger, stupor, coma, and finally respiratory and cardiac failure. Since that time the association of these
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symptoms with certain metabolic disorders that give rise to an acidosis have been well recognized clinically. However, in these cases where an acidosis exists as a secondary factor based upon some primary pathological condition, it has always been a problem as to how much of the symptomatology was due to the acidosis and how much was due to other derangements.

For this reason the general symptomatology of these patients in whom a simple acidosis was produced for a considerable period by acid feeding, was carefully noted. The distress that occurred in most cases, if acid intoxication was carried sufficiently far, developed approximately in the following order: loss of appetite, lassitude, listlessness, headaches, weakness, nausea, occasionally vomiting, symptoms of dehydration, muscular aches and pains and abdominal cramps, loss of weight, hyperpnea, drowsiness, and renal insufficiency. The order is, of course, approximate only, for often the several different types of distress may come on at the same time and in some cases the sequence may be considerably changed.

Loss of Appetite.—This condition developed in all of the eleven acidosis cases and usually came on during the first few days of mild acidosis and then improved, but later returned more markedly as the acidosis became severe. The first period of anorexia was probably more related to the disagreeableness of taking the acids or salts by mouth and the resulting temporary purgation, than to the acidosis itself. Adjustment then seemed to take place and for a period of a week to 10 days the appetite was fairly good, even though the blood pH gradually decreased from 7.30 to below 7.25. Finally, however, with the general marked depression, the appetite failed completely and all food was refused.

Lassitude, Listlessness, Drowsiness, and Stupor.—In general, as the blood pH dropped from normal to 7.30 or lower in the course of the first 3 or 4 days, the subject gradually became disinclined toward any activity and lost interest in his surroundings. This condition gradually increased as the acidosis progressed. In general, the acid medication was stopped before this distress became marked but in a few cases the lassitude and listlessness progressed to definite drowsiness as the blood pH dropped below 7.20 after being low for a period of a week or 10 days. In several of these cases mental dullness, especially the inability to concentrate,
became very pronounced. This was especially noticeable in the cases of A. K-r and H. S-l (Fig. 9) where an attempt was made to carry on mental work each day.

Headaches.—Generalized, dull headaches occurred in a majority of the subjects with severe acidosis although the occurrence was usually inconstant and irregular. Any slight effort usually initiated a headache and as the acidosis progressed this distress would usually come on spontaneously and persist for days. The headaches were probably a secondary result from the general debility, although a cerebral edema secondary to depressed oxidation might also have played a rôle.

Weakness.—Fatigability and weakness are usually noticed after 3 or 4 days of mild acidosis and gradually increase in severity as the acidosis progresses. The ease of fatigue is more pronounced than the loss of strength. This is well exemplified by the observation that normal strength may be exhibited in flexion of the forearm but if this movement is repeated several times marked fatigue develops. This probably is due to the development of a still more severe tissue acidosis due to CO₂ accumulation as a result of the poor CO₂-carrying power of the blood. Loss of muscular power as well as endurance, however, develops as the acidosis becomes severe and prolonged.

Dehydration.—In practically all cases it was noticed that as the acidosis progressed, it was more and more difficult to obtain blood samples from the veins of the cubital region of the arm. Not only did the skin and subcutaneous tissue seem to lose their turgor and normal consistency, but the veins seemed definitely less prominent. Dryness of the mucous membranes could be noted and the patients frequently complained of dryness of the mouth. There was also a distinct loss of weight amounting usually to 2 to 3 kilos during the period of the acidosis, the greater portion of which usually was lost during the first 4 or 5 days. This period of rapid loss usually was coincident with that of the initial diuresis and purgation. If reduced food intake or autolysis of tissue proteins due to decreased pH were the cause of weight loss, it would be expected that the greater loss would occur during the latter period of severe acidosis. The loss in weight during CaCl₂ ingestion was first noted by Blum (10) and his coworkers who used this salt successfully in the treatment of edema. They also
noted a distinct concentration of the plasma proteins during the first few days when diuresis occurred. These workers attributed the loss of water to the effect of calcium but Haldane, Hill, and Luck (5) showed that a similar dehydration occurred when NH₄Cl was ingested. The explanation of these latter workers that the loss of water is due to the acidosis itself is probably correct. They state: "The increased acidity brings the blood and tissue proteins nearer to their isoelectric points, and they therefore release cations which they are holding in Donnan equilibrium, and diminish their osmotic pressure, thus losing water."

The introduction of the Donnan equilibrium is not clear, for the effect is probably one of decreasing protein dissociation and therefore the ability to unite chemically with cations, but the end-result as far as dehydration is concerned is the same. Later it will be shown that alkalosis has the opposite, that is, hydrating effect.

Muscular Aches.—Haldane and his coworkers (5) noted that CaCl₂ produced great general discomfort, pains in the head, limbs, and back. They state that these effects never occur with NH₄Cl and must be attributed to the calcium. In our experience, these muscular aches and pains came on in a majority of our severe acidosis cases, whether caused by CaCl₂, NH₄Cl, or H₃PO₄ ingestion. Exertion seemed especially to be a predisposing factor in bringing on these pains and in one case severe aches and spasm resulted in the muscles of the legs after slight exertion. These were similar to the ordinary muscle cramps occasionally experienced after severe exercise. In both cases the condition is probably due to the acidosis or its secondary effect upon metabolism.

Air-Hunger.—This condition, usually associated by the clinician with acidosis, was not present in any of these cases in the degree of acidosis obtained while the patient was at complete rest. Slight exertion, however, usually brought it on. Clinically, of course, more severe acidoses are seen, occasionally below pH 7.00 and air-hunger then may be a striking feature.

Renal Insufficiency.—Only one of our cases developed temporary renal insufficiency (P. M-n, Experiment 9) and we have seen several more since where no renal incompetency was apparent before. In all these cases NH₄Cl was administered and the question arises whether the extra amount of ammonia to be excreted was a factor in renal impairment and nitrogen retention.
Symptomatology During Alkalosis.—That the symptoms of acidosis and alkalosis may be quite similar is now being generally appreciated. In our study, practically every symptom elicited during acidosis was also noted during alkalosis; namely, loss of appetite, lassitude, listlessness, headaches, weakness, nausea, and drowsiness. Renal insufficiency, especially where some impairment existed previously, has been reported in the literature (11). Air-hunger, stupor, and irrational mental states were of course not observed in the cases reported here but these conditions have been observed where the diagnosis of alkalosis was definitely established and disappeared when the blood reaction was restored to normal (12). Symptoms of dehydration, however, are not present in alkalosis as contrasted with acidosis, in fact, there usually is definite evidence of hydration. The edema developing after excessive NaHCO₃ administration so frequently observed is an example of this disturbance in the water balance. All of our patients, whether given NaHCO₃ or Na citrate, showed an increase in weight from 0.90 to 3.3 kilos. In the case of P. M-n, Experiment 14, where there was only a slight increase and finally a loss in weight, his general condition was poor and there was marked anorexia. Undoubtedly poor nutrition was a definite factor in counteracting the apparent effect of hydration as far as weight was concerned. Although the edema of NaHCO₃ ingestion has been looked upon as due to Na retention, the primary effect is probably related to the increased pH and its influence on the protein-salt osmotic effect, as described under dehydration in acidosis. It is logical to assume that the same reason that causes dehydration in acidosis causes hydration in alkalosis.

That the subject with alkalosis is especially sensitive to anoxemia has already been mentioned. His susceptibility to fatigue is markedly increased and exercise increases most of his distress, especially headache and lassitude. In general it would be expected that the acids liberated during exercise would diminish the alkalosis and the accompanying distress. This neutralizing effect cannot be appreciable, especially in view of the large alkali reserve, and it must be assumed that the alkalosis has a depressing effect on the metabolism of exercise.
Relation of Acidosis and Alkalosis to General Metabolism.

It is readily seen that the general well being and functional activity is at its optimum at the normal reaction of the body and that a depression occurs with a variation of the pH in either direction. Restlessness, lassitude, debility, fatigability, headaches, listlessness, and finally stupor are symptomatic reactions of both acidosis and alkalosis. These are, however, also the usual reactions associated with depression of the energy metabolism as in chronic anoxemia as obtained at high altitudes, carbon monoxide poisoning, methemoglobinemia, cyanide poisoning, marked anemia, hypothyroidism, etc. In earlier work we have already shown that in death by anoxemia, life can be greatly prolonged by maintaining a normal reaction of the blood; that variation in either the direction of acidosis or alkalosis shortens life (13). It has also been shown that in tissue oxidation in vitro, the rate of oxygen consumption apparently is at its optimum at approximately the normal blood reaction with a depression in either direction. It is possible that the ill effects of acidosis and alkalosis are produced through the common channel of depression of tissue oxidation. This conception would explain the similar symptomatic effects of two apparently separate and opposite conditions.

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SUMMARY.

An acidosis of blood pH 7.30 to 7.20 can readily be produced and maintained for a period of several weeks by the ingestion of \( \text{H}_2\text{PO}_4 \), \( \text{NH}_4\text{Cl} \), \( \text{CaCl}_2 \), \( (\text{NH}_4)_2\text{HPO}_4 \) or combinations of these substances.

An alkalosis of blood pH 7.50 to 7.55 can be maintained for several weeks by the administration of \( \text{NaHCO}_3 \) or Na citrate.

In normal individuals recovery from this grade of acidosis or alkalosis is rapid and usually complete in 24 to 48 hours.

The symptomatic distress during acidosis or alkalosis is similar; namely, lassitude, nausea and later vomiting, anorexia, headaches,
weakness, listlessness, muscle aches, and drowsiness. A case of renal involvement was noted both in acidosis and alkalosis. Opposite effects apparently are obtained in regard to weight and hydration; during acidosis there is decrease in weight with signs of dehydration, while during alkalosis there is evidence of hydration with increase in weight. There seems to be a slight increase in ventilation during alkalosis.

The change in total venous blood CO$_2$ during acid or alkali ingestion parallels that of blood pH closely as long as there is no renal involvement or respiratory upset.

The CO$_2$ tension of the venous blood has a tendency to decrease slightly during acid ingestion but in general does not change markedly, while the CO$_2$ tension of the arterial blood drops quite appreciably. During alkali ingestion the venous blood CO$_2$ tension does not change to any extent.

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