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Pathological Significance, Diagnosis and Treatment of Acidosis

By

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Many aspects of the disorders of acid—base balance are being reinterpreted these last years. The main problems discussed are (i) the relation of clinical symptoms to the degree of acidosis; (ii) the terminology, involving also some basic principles; (iii) the parameters used for the evaluation of disorders; (iv) the treatment of choice of the various disturbances.

In this paper some aspects of the above problems will be discussed on the basis of the literature and of our own experience in the field of acidosis in some paediatric conditions.

(*i*) Relation of Clinical Symptoms to Degree of Acidosis

Knowledge about the symptomatology and the pathologic significance of acidosis dates back to more than ninety years when KUSSMAUL [12] described the "terminal" dyspnoea arising in diabetic coma. A few years later, in 1877 WALTER [25] studied acid intoxication in animals and discovered its relation to the blood bicarbonate, to dyspnoea and to the terminal circulatory collapse. STADELMANN [23] in 1883 first emphasized the analogy between experimental acid intoxication and diabetic coma, while CZERNY [4] in 1897 interpreted "alimentary toxicosis" of infants as an acidotic coma.

The extreme abnormal variations for plasma pH compatible with life ranges between 7 and 7.8 according to PETERS and VAN SLYKE [17]. More recent reports describe, however, survival at lower values. KETY's [11] patient exhibiting an arterial pH of 6.8 recovered, and so did our two patients with diabetic coma showing pH values of 6.86 and 6.89, respectively, and half of our prematures exhibiting pH values between 6.9 and 7 also survived. The lowest value recorded in our material was in a premature infant suffering from a mixed disturbance i.e. diarrhoeic and respiratory acidosis, who 3½ hours preceding death exhibited a pH of 6.46. The lowest pH compatible with survival in acute experiments of short duration in dogs appears to be 6.4 [3].

Were it not for the "respiratory compensation", the acid loads imposed on body buffers of the extent occurring in many pathologic conditions

would frequently depress the pH below the dangerous threshold value of 7. Fig. 1 visualizes the powerful effect on the pH of this defense mechanism in diabetic and in diarrhoeal acidosis of prematures.

pH values calculated under the assumption of an unchanged pCO_2 of 40 mm Hg, compared to the pH values measured directly, indicate a compensation of 0.4 and 0.29 units, respectively. In the lack of this adjustment all the pH values would have fallen below 6.8 i.e. the lowest value recorded in survivors of acidosis. With this state of affairs we are somewhat reluctant to join the opinion of SINGER and HASTINGS [21]: "there is no evidence to suggest that a state of normal pH and low pCO_2 is better tolerated by the body than one of low pH-s and normal pCO_2 and hence that one state should be called compensated and the other uncompensated." We feel that the time-honoured term of "respiratory compensation", though admittedly of teleological by-flavour, should not disappear from clinical medicine.

The greatest danger of metabolic acidosis is the superimposition of respiratory acidosis. Fig. 2. shows a case of the mixed type of acidosis, i.e. diarrhoeal acidosis complicated by CO_2 retention due to bronchiolitis.

When the case was first studied, the metabolic acidosis was compensated by a fall of pCO_2 to 18.4 mm Hg. Subsequently metabolic acidosis increased, and pCO_2 rose to 70 mm Hg resulting preterminally in a pH 6.46, the lowest pH recorded in our material. If pCO_2 could have been maintained at the previous level of 18.4 mm Hg, pH would have fallen only to 7.0.

The correlation of the clinical symptoms with the degree of acidosis is difficult since acidosis in most clinical cases is but one of the many simultaneous changes in body fluid homeostasis. The relationship between hyperpnoea and pH, although complex, appears to be the most convincing. Hyperventilation begins according to KETY [11] at a threshold of about pH 7.2, it has its maximum in the region of pH 7.0, and falls off at lower values. Following treatment, however, respiratory response lags behind the response of pH, and hyperpnoea may continue for a time after the correction of the pH.

Unconsciousness and decrease in cerebral O_2 consumption in diabetic coma appears to be in closer relation to the concentration of ketoacids than to pH [11]. In diarrhoeal dehydration of infants unconsciousness may arise at any pH value since it appears to be more dependent on the degree of cerebral hypoxia than on acidosis [10]. In our material contact could be established with patients exhibiting pH values down to 7.04, while below 7, all patients were unconscious.

In the electroencephalogram the potentials become depressed with the severity of acidosis. In the dog if the arterial pH falls to 6.6 the recordable potential falls to zero. No animal survived if the brain waves were absent for more than twenty minutes [3].

One important factor limiting survival seems to be myocardial failure:

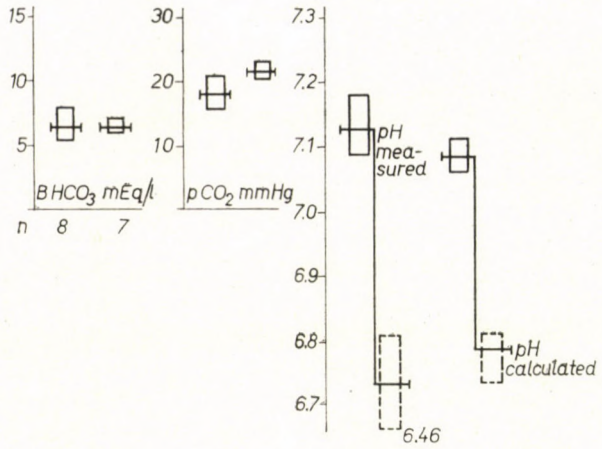

FIG. 1. The effect of respiratory compensation on pH in diabetic and in diarrhoeal acidosis. The left side of each pair of columns represents values found in diabetic, the right in diarrhoeal acidosis. The vertical line between "pH measured" and "pH calculated" represents the extent of respiratory compensation in pH-units

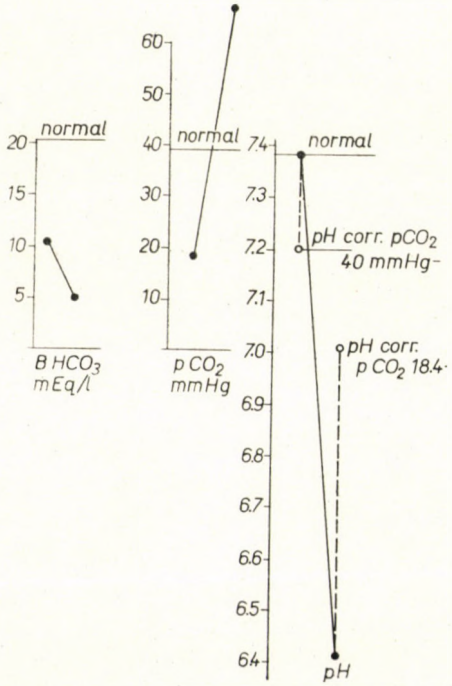

FIG. 2. Effect of the superimposition of respiratory acidosis on metabolic acidosis. Explanation in text

Using an isolated rat-heart preparation OPIE [15] found no detectable effects on the amplitude of left ventricular contraction, the ECG, and the glucose metabolism of the heart in the pH range 7.1 to 8.0. At pH 6.9, however, gross impairment of cardiac conraction set in. The human myocardium may, according to CLOWES [3] survive at a pH of 6.8.

In an important work on asphyxiated immature lambs DAWES [5] showed that anaerobic glycolysis results in the accumulation of lactic acid while the consequential fall in pH inhibits glycolysis. A high rate of glycolysis can, however, be maintained and survival prolonged by infusing glucose and base simultaneously. A further potential danger of acidosis is the rise in plasma potassium concentration.

Although immediate danger to life appears to arise only at pH values below 7, the activity of some enzymes may be affected by smaller changes. The duration of acidosis is also of obvious importance.

Chronic acidosis may interfere with growth and development, and seems to have an aetiologic role in the genesis of renal dwarfism [26].

(*ii*) TERMINOLOGY

The well-known diagram of GAMBLE [7] had for forty years an almost unparalleled influence on the teaching and the conceptions of clinical physiologists working in the field of acid—base disturbances. The basis of his conception was the principle of electrical neutrality. The value of bicarbonate, the "adjustable anion", emerges from his diagram as the result of the interplay of the sum of the cations versus the sum of anions of the blood plasma. The former he called "fixed bases", the latter, according to contemporary usage, "acid radicles" (= "Säurerest"). From the diagram it could be deduced that chloride excess can displace bicarbonate while hypochloraemia has an opposite effect. However, the diagram, this didactic masterpiece, was not constructed to imply directly acting biochemical mechanisms, i.e. a reduction or expansion of bicarbonate by chloride, but simply to indicate obligatory relationships in terms of electroneutrality.

This conception as part of GAMBLE's brilliant work on dehydration certainly was the starting point of great discoveries and also served as guide in the planning of the treatment of disturbances. His nomenclature, however, is not in keeping with actual biochemical terminology. It is now generally agreed that an acid should be defined according to BRONSTEDT [2] and LOWRY [13] as a substance that can lose a hydrogen ion, thus forming a base, while, conversely, a base is a substance which can gain a proton thus forming an acid. An acid (HA) dissociating in water forms the anion A, which as a proton acceptor is to be considered a base, while H_2OH^+ is to be considered a base, while H_2OH^+ is the proton donor or acid: $HA + H_2O \leftrightarrows H_2OH^+ + A^-$. Thus, sodium and potassium ions should not be called bases nor chloride an acid, but simply kations and anion, respec-

tively. Furthermore, it is clear that changes in acid—base parameters are the immediate effects of balances of H-ions, while changes of chloride concentration relative to sodium do not affect directly the value of bicarbonate. Loss of H- and Cl-ions in gastric juice is accompanied by a simultaneous "infusion" of HCO'_3 in the blood, while in diarrhoea loss of bicarbonate occurs with a simultaneous delivery of H-ions to the extracellular fluid.

While fully acknowledging the immediate and central role of H-ion in actuating changes in acidity, the description of these events exclusively in terms of hydrogen ion leaves us with an incomplete picture. The principle of electroneutrality still holds true. To quote Darrow, "sodium, chloride and bicarbonate of extracellular fluids have obligatory relationships that can be described in terms of volume and concentration".

The role of chloride, the leading structural anion of the extracellular fluid, which has almost been forgotten with the attention focussed now on the hydrogen ion, is being reestablished in a series of brilliant works by SCHWARTZ et al. [19, 8]. They have shown that chloride as well as other anions play an important role in acid — base regulation not by directly displacing or raising bicarbonate but by altering renal hydrogen ion secretion.

The mere fact that chloride plays a critical role in the correction of practically all types of hypochloraemic alkalosis [8] shows that to think in terms of hydrogen ions alone excluding the classical kations and anions does not satisfy the needs of either the clinician or the physiologist.

(*iii*) PARAMETERS USED IN THE EVALUATION OF DISTURBANCES

The ideal parameters for the evaluation of acid—base disturbances should comply with the following requirements.

1. Provide a clear separation of the respiratory and metabolic factors in complex clinical states, thus to distinguish "simple" disturbances in which there is a single primary aetiological factor with or without compensatory phenomena, from "mixed" disturbances in which two primary i.e. aetiological factors are present simultaneously.

2. Define or reflect the changes that occur in the whole body and thus serve as a quantitative basis of treatment.

3. Be technically simple, easily suitable for serial measurements to control in short intervals the results of treatment.

The classical parameters used in clinical physiology are the pCO_2, expressing the "respiratory", and HCO'_3 the "metabolic" component of acid—base balance, while pH reflects the combined influence of both factors. Since the accumulation of acids or bases elicits secondary "compensatory" changes in pCO_2 and HCO'_3 also varies with pCO_2, new parameters have been proposed in order to give a direct measure of the accumulation of acids or bases in the organism.

The whole blood buffer base of SINGER et al. [21, 22] is the sum of the

milliequivalents per liter blood of the buffer anions: bicarbonate, haemoglobin, protein and phosphate. The advantage of this parameter lies in the exclusion of the effects of changes in pCO_2. The same holds true for the "base excess" of ASTRUP [1], which gives directly in mEq/l of whole blood the pathologic surplus amount of fixed acids or bases. ASTRUP's "standard bicarbonate" again excludes the influence of varying pCO_2 on bicarbonate. It measures the concentration of bicarbonate in blood plasma after oxygenated whole blood has been equilibrated with CO_2 at the normal pCO_2 of 40 mm Hg.

The advantage of these newer parameters over the classical ones has been challenged by SCHWARTZ and RELMAN [18]. Firstly they are not convinced that titration curves of whole blood with varying pCO_2 *in vitro* would correspond to the conditions *in vivo*, in other words that they should be valid for the body as a whole. Secondly in chronic respiratory disturbances compensatory changes of HCO'_3 induce changes in base excess and in standard bicarbonate, exceeding values predictable from changes measured *in vitro*. Such phenomena lead to some confusion in terminology since the compensatory increase in bicarbonate occurring in respiratory acidosis is called by some authors a complicating "alkalosis", while decrease in bicarbonate in respiratory alkalosis was referred to as a secondary "metabolic" acidosis. Were this terminology accepted at its face value, it could lead to erroneous treatment of the compensatory changes. The situation would be even more complex if real "primary" metabolic disturbances were superimposed on chronic compensated "primary" respiratory disturbances. SCHWARTZ and RELMAN concluded that "diagnosis of a complex disturbance does not follow automatically from any one laboratory datum". Every parameter has to be appreciated and interpreted in the light of full knowledge of the patient and of the physiologic phenomena underlying the changes observed in the blood constants. This "physiologic approach" [18] requires a good deal of clinical experience and the knowledge of the physiological patterns of the various disturbances encountered in clinical situations.

The best parameters, no matter whether the new or the classical ones, are those with which the person in charge of the patient has gained the widest clinical experience. We now use ASTRUP's parameters since this method permits to follow and control the effects of the treatment with ease.

(*iv*) NOTES ON THE TREATMENT OF ACIDOSIS

Calculations of the amount of bicarbonate required to correct acidosis were already proposed by PALMER and VAN SLYKE [16] in 1917. They recommended that deficits should be corrected by giving per kg body weight an amount of acid or base, respectively, corresponding to $0.7 \times \triangle$ mEq total $-CO_2$ of plasma. In other words 0.7 mEq of bicarbonate should be infused to raise plasma bicarbonate by

one mEq/l. Using these amounts secondary alkalosis due to overcorrection is a frequent complication. MELLEMGAARD and ASTRUP [14] argue that calculations of the initial dose should be based on the size of deficits or surpluses only in the extracellular space. They suggest the formula, 0.3× base excess in mEq/l blood per kg body weight. The subsequent doses depend on the result of treatment as controlled by frequent analyses. This amount is about half of that used by PALMER and VAN SLYKE and is in keeping with the recommendations of SINGER et al. [22] who give an amount of 0.35 mEq of bicarbonate for each mEq of bicarbonate deficit in blood plasma.

In applying these recommendations we have again to emphasize the importance of the "physiological approach".

The amount of pathologio acids retained in the body may rapidly change with therapeutic procedures aimed at improving circulation, renal function and the oxydation of acids. In such cases less bicarbonate than calculated will ultimately suffice for neutralizing the negative base excess existing in the extracellular fluid. In other cases, more than the expected amounts of acid can be generated or retained. In young infants, especially in prematures, we must also consider that extracellular fluid occupies a larger proportion of the body than in adults.

Fig. 3 shows the amounts of bicarbonate needed in various acidotic conditions during the first 24 hours of treatment to raise plasma pH above 7.3 and to decrease base excess to moderate values.

The corresponding values for standard bicarbonate before treatment and at the end of the first 24 hours are shown in Table I.

In the acute emergency of diabetic coma the amount of bicarbonate administered in 24 hours is somewhat higher than the "initial" dose recommended by MELLEMGAARD and ASTRUP, while, owing to favourably progressing oxidation and renal elimination of acids, much less proved to be sufficient in severe diabetic acidosis. In the three hopeless cases of uraemia, exhibiting NPN values of about 200 mg per 100 ml, no renal elimination or oxidation of acids was possible. In this "closed system", infusion of the prescribed "initial dose" left us with a considerable base excess of 11.4 mEq/l, and the pH of 7.34 was in part due to persisting hyperventilation. In ketonaemic vomiting we used no bicarbonate at all since saline-glucose solution by promoting the oxidation of acids and by correcting dehydration proved to be sufficient for correcting the acidosis. It should be noted that in these conditions intensive bicarbonate treatment, as practised in France, frequently leads to considerable iatrogenic alkalosis and hypokalaemia [6, 9]. This effect can be predicted by the use of a half forgotten parameter, the "potential bicarbonate" [20], the amount of bicarbonate generated by the relative excess of sodium over chloride when the retained acids depressing the bicarbonate are burned.

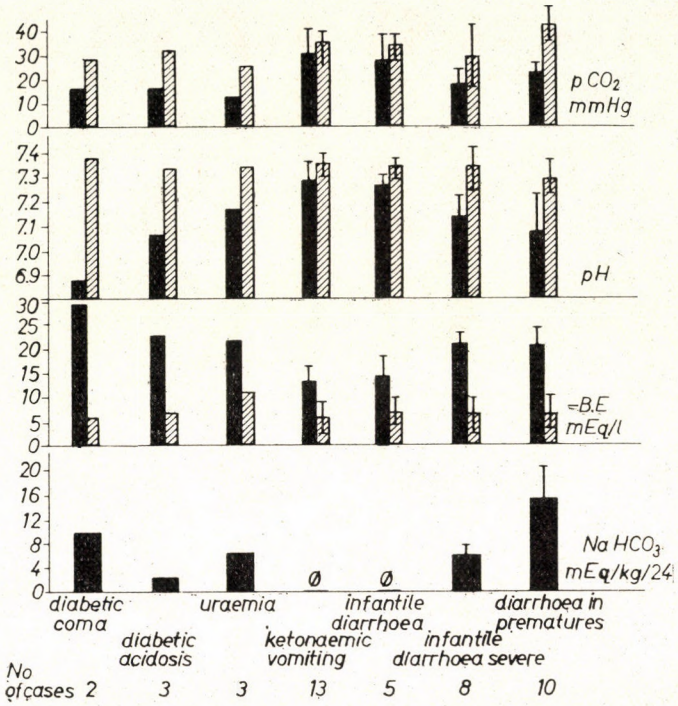

FIG. 3. Amounts of $NaHCO_3$ needed during the first 24 hours of treatment to raise the pH above 7.3 in various acidotic conditions. The left side of each pair of columns shows the pretreatment values, the right side the values measured at the end of the first 24 hours. For further details see text

TABLE I

	No. of cases	Standard bicarbonate mEq/l		Bicarbonate administered mEq/kg/24h
		initial	end of first 24 hours	
Diabetic coma	2	5.5	16.1	9.6
Diabetic acidosis	3	8.4	18.3	2.1
Uraemia	3	8.6	15.1	6.1
Acetonaemic vomiting	13	14.4±2.6	20.3±2.6	0
Diarrhoea in infants, moderate	5	13.5±2.6	18.4±2.5	0
Diarrhoea in infants, severe	8	8.6±2.3	16.6±3.4	5.8±1.4
Diarrhoea in prematures	10	9.7±2.4	18.2±3.0	15.0±5.8

In such situations bicarbonate administration inevitably leads to alkalosis and potassium loss since, to express events in modern terminology, low chloride relative to sodium should raise the renal threshold of bicarbonate [8, 9]. Bicarbonate treatment also proved to be superfluous in diarrhoeal

acidosis of moderate severity. Acidosis in diarrhoea is complex in origin; enteral loss of bicarbonate, generation of acids in the gut due to fermentation of non-absorbed carbohydrates [24], and renal retention of acids due to shock seem to be the main aetiologic factors. These processes may favourably be influenced by rehydration and withholding food. Since these inechanisms operate slowly, more severe cases require an immediate neutralization of acids. The "initial" dose recommended by MELLEMGAARD and ASTRUP proved to be sufficient for the first 24 hours in the majority of older infants. Prematures occupy a special position, requiring surprisingly high amounts of bicarbonate. The average dose was 15 mEq/kg, although base excess and standard bicarbonate were about the same as in severe diabetic acidosis or in severe diarrhoea of older infants. The maximal amount given in the first 24 hours was 24 mEq/kg, about four times the amount of the "initial dose" calculated from the negative base excess. The reasons for this high bicarbonate requirement are not quite clear. Larger extracellular space appears to be but one of the factors concerned. It should also be stressed that premature acidosis shows a conspicuous tendency to relapse. Some cases needed large doses of bicarbonate for ten or more days.

SUMMARY AND CONCLUSIONS

The correlation of the clinical symptoms with the degree of acidosis; the lowest values of pH compatible with survival; and the choice of the various parameters serving as the basis of treatment have been reviewed. The amounts of bicarbonate required to correct acidosis in various disturbances including diabetic coma and acidosis, uraemia, ketonaemic vomiting, diarrhoea in older children and in prematures, were reported. It has been pointed out that bicarbonate requirements depend on the peculiarities of the physiological basis of acidosis in the given case and not only on the extent of acid accumulation as measured by $\triangle$ plasma bicarbonate or the value of negative base excess. If there is a fair possibility that oxydation and/or diminution of acids can rapidly be enhanced by treating the primary disturbance leading to acidosis, bicarbonate treatment is superfluous, provided the base excess does not exceed 12 mEq/l. In ketonaemic vomiting it is even harmful for it may cause secondary alkalosis and hypopotassaemia. If the base excess does not exceed 20 mEq/l and pH is not lower than 7.1, the "initial doses" recommended by MELLEMGAARD and ASTRUP mostly prove to cover requirements for the first 24 hours in diarrhoeal as well as in diabetic acidosis. Premature infants should, however, never be treated without bicarbonate, and the doses should be three to four times higher than those needed in any other acidotic condition of comparable severity.

The fundamental requirement of a successful treatment of any acidotic condition is the frequent laboratory control of the sometimes unpredictable post-therapeutic developments.

References

1. Astrup, P., Siggaard Andersen, O., Jorgensen, K., Engel, K.: The acid-base metabolism. A new approach. Lancet, **1,** 1035 (1960).
2. Bronstedt, J. N.: The conception of acids and bases. Rec. Trav. chim. Pays-Bas **42,** 718 (1923).
3. Clowes, G. H. A., Hopkins, A. L., Simeone, F. A.: A comparison of the physiological effects of hypercapnia in the production of cardiac arrest. Ann. Surg. **142,** 459 (1955).
4. Czerny, A.: Zur Kenntnis der Gastroenteritis im Säuglingsalter. IV. Respirationsstörungen. Jahrb. Kinderheilk. **45,** 271 (1897).
5. Dawes, G. S., Mott, J. C., Shelley, H. J., Stafford, A.: The prolongation of survival time in asphyxiated immature foetal lambs. J. Physiol. (Lond.) **168,** 43 (1963).
6. Debré, R., Royer, P., Lestradet, H.: Metabolic significance of nervous symptoms due to attacks of vomiting with ketosis in children. J. Pediat. **48,** 409 (1956).
7. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Harvard University Press, Cambridge, Mass. 1947.
8. Kassirer, J. P., Berkman, P. M., Lawrenz, D. R., Schwartz, W. B.: The critical role of chloride in the correction of hypokalemic alkalosis in man. Amer. J. Med. **38,** 172 (1965).
9. Kerpel-Fronius, E.: Iatrogenic damage in fluid replacement therapy. Triangle **6,** 217 (1964).
10. Kerpel-Fronius, E., Varga, F., Kovách, I., Kun, K.: Cerebral anoxia in infantile dehydration. Arch. Dis. Childh. **25,** 156 (1950).
11. Kety, S. S., Polis, B. D., Nadler, C. S., Schmidt, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. clin. Invest. **27,** 500 (1948).
12. Kussmaul, A.: Zur Lehre vom Diabetes mellitus. Über eine eigentümliche Todesart bei Diabetikern. Dtsch. Arch. klin. Med. **14,** 1 (1874).
13. Lowry, T. M.: The uniqueness of hydrogen. Chem. and Ind. **42,** 43 (1923).
14. Mellemgaard, K., Astrup, P.: The quantitative determination of surplus amounts of acid or base in the human body. Scand. J. clin. Invest. **12,** 187 (1960).
15. Opie, L. H., Kadas, Th. Gewers, W.: Effect of pH on the function and glucose metabolism of the heart. Lancet **2,** 553 (1963).
16. Palmer, W. E., Van Slyke, D. D.: Studies in alkalosis IX. Relationship between alkali retention and alkali reserve in normal and pathological individuals. J. biol. Chem. **32,** 499 (1917).
17. Peters, J. P., Van Slyke, D. D.: Quantitative Clinical Chemistry. Vol. I. Williams and Wilkins. Baltimore 1932.
18. Schwartz, W. B., Relman, A. S.: A critique of the parameters used in the evaluation of acid-base disorders. New Engl. J. Med. **268,** 1382 (1963).
19. Schwartz, W. B., Hays, R. M., Polak, A., Haynie, G. D.: Effects of chronic hypercapnia on electrolyte and acid-base equilibrium, II. Recovery, with special reference to the influence of chloride intake. J. clin. Invest. **40,** 1238 (1961).
20. Seldin, D. W., Tarail, R.: The metabolism of glucose and electrolytes in diabetic acidosis. J. clin. Invest. **29,** 552 (1950).
21. Singer, R. B., Hastings, B.: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine **27,** 223 (1948).
22. Singer, R. B., Clark, J. K., Barker, E. S., Crosley, A. P., Elkinton, J. R.: The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. Medicine **34,** 51 (1955).
23. Stadelmann, R.: Über die Ursache der pathologischen Ammoniakausscheidung beim Diabetes mellitus. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. **17,** 419 (1883).
24. Torres-Pinedo, R., Lavastida, M., Rivera, C. L., Rodriguez, H., Ortiz, A.: Studies on infant diarrhea. I. A comparison of the effects of milk feeding and intravenous therapy upon the composition and volume of the stool and urine. J. clin. Invest. **45,** 469 (1966).
25. Walter, F.: Untersuchungen über die Wirkung der Säuren auf den thierischen Organismus. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak. **7,** 148 (1877).
26. West, C. D., Smith, W. C.: An attempt to elucidate the cause of growth retardation in renal disease. Amer. J. Dis. Child. **91,** 460 (1956).

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