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ACIDOSIS AND ALKALOSIS: A MODERN VIEW

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With respect to the interrelations of acids and bases in mammalian organisms the maintenance of the hydrogen ion concentration within a rather narrow range appears to be of paramount importance. Secondary, or ancillary to this, but of nearly equal importance, is the mechanism by which future or potential disturbances of the acid: base equilibrium may be rectified. Remarkable progress has been made in unravelling the exceedingly complex processes which are involved, but until recently the work has undoubtedly been hampered by the use of concepts concerning the nature of acids and bases which, though in accord with our knowledge at the time they were introduced, have since been superseded by the simpler ideas now generally accepted by physical chemists. We believe that the application to biochemistry of these ideas, and the terminology based upon them, is capable of clarifying the subject of hydrogen ion regulation and, consequently, of acidosis and alkalosis. In particular, it emphasizes the role of the bicarbonate ion, it facilitates understanding of the renal mechanism, and it affords an explanation of the secondary but important role of metallic cations such as sodium and potassium which are neither bases nor acids, and of anions such as chloride which are not effective bases. This paper is an attempt, brief and necessarily incomplete, to base a description of acidosis and alkalosis upon chemically acceptable definitions of acids and bases.

ACIDS AND BASES

An "acid" is defined, according to the theory independently enunciated by Lowry and Brönsted, as a substance which, in solution, tends to liberate hydrogen ions (protons); these hydrogen ions may remain as such, or may combine with the solvent forming, e.g., hydroxonium ions, H_3O^+, or may combine with negatively charged ions. A "base" is similarly defined as a substance which tends to accept hydrogen ions.

Since the dissociation of an acid is reversible, the negatively charged anion which is liberated along with the hydrogen ion is a base, and the older term "acid radicle" for such an anion is misleading.

$$\underset{\text{(Acid)}}{H^+ \text{ donor}} \rightleftharpoons H^+ + \underset{\text{(Base)}}{H^+ \text{ acceptor}}$$

Acids, though frequently undissociated molecules, are not necessarily so, and bases, though the class includes all anions, may be molecules. Thus the cation NH_4^+ liberated from ammonium salts is an acid because it is capable of producing hydrogen ions according to the equation:

$$NH_4^+ \rightleftharpoons H^+ + NH_3$$

From this equation it is evident that the ammonia molecule NH_3 is a base. Similarly the anion $HPO_4^=$ is a base because it can accept H^+ to form $H_2PO_4^-$ which can accept more H^+ to form the acid molecule H_3PO_4. But the anions $H_2PO_4^-$ and $HPO_4^=$ are also acids because they can lose H^+ to form, ultimately, the base $PO_4^{\equiv}$; they are "amphoteric."

These definitions leave undisturbed many of the familiar concepts. Thus the acidity or alkalinity of a solution is still expressed in terms of hydrogen ion concentration or of *p*H, the logarithm of its reciprocal.

They emphasize the fact that the acidity of a solution does not depend solely on the concentration of acid present but also on the degree of dissociation. A decimolar solution of hydrochloric acid (almost completely dissociated) has a much greater acidity than a decimolar solution of acetic acid only about 2% dissociated.

They permit us to deduce from the equation: $HX \rightleftharpoons H^+ + X^-$ the standard formula: $pH = pK + \log_{10}\frac{[\text{Base}]}{[\text{Acid}]}$.* They avoid the confusion which arises from the common misconception that anions are acids and that metallic cations are bases. This does not mean that cations such as

*The symbol [X] represents the concentration of X expressed in g. ions or g. molecules (as the case may be) per litre of solution.

Na^+ and K^+ are of no importance, but it does make it clear that they are not primary regulators of the acid : base equilibrium. Their importance—apart from any special functions of their own—is that electrical neutrality must always be maintained ; anions and cations must always be present in equal concentrations, and a " cation-anion imbalance," to which some writers refer, can never, in fact, occur.

The " strength " of an acid is measured by its tendency to donate hydrogen ions or, in other words, by its degree of dissociation ; the freely dissociated mineral acids (HCl, etc.) are strong acids ; slightly dissociated acids such as carbonic acid are weak. Similarly a strong base has a great affinity for hydrogen ions whereas a weak base is a poor acceptor. The important corollary of this latter fact is that the anion of a strong acid is a weak base, e.g., Cl^-, and the anion of a weak acid is a strong base, e.g., HCO_3^-, OH^-. The physiologically important acids can, on this basis, be arranged in decreasing order of strength, and if this is done as in Table I the corresponding bases are automatically arranged in increasing order of strength.

TABLE I

ACIDS IN ORDER OF DECREASING AND BASES IN ORDER OF INCREASING STRENGTHS

Acid		Base
HCl	$\rightleftharpoons$	$H^+ + Cl^-$
$H_2PO_4^-$	$\rightleftharpoons$	$H^+ + HPO_4^=$
H_2CO_3	$\rightleftharpoons$	$H^+ + HCO_3^-$
HPr*	$\rightleftharpoons$	$H^+ + Pr^-$
NH_4^+	$\rightleftharpoons$	$H^+ + NH_3$
H_2O	$\rightleftharpoons$	$H^+ + OH^-$

* Under physiological conditions nearly all proteins are actually ions which are, like $H_2PO_4^-$, still donors of H^+. Some of these proteins are actually rather stronger acids than H_2CO_3, some weaker.

BUFFERS

A " buffer system," which minimizes *p*H changes on addition of acid or base, consists of a solution containing a weak acid together with one of its soluble salts. The acid, being weak, is slightly ionized ; the soluble salt, however, is ionized to a large extent. The mixture thus provides a reservoir of base (anions) which can combine with added H^+, i.e., " neutralize " added acid, and a reservoir of acid (undissociated acid molecules) which can donate hydrogen ions to neutralize added base. Thus a mixed solution of carbonic acid and sodium bicarbonate acts as a buffer system. It contains undissociated carbonic acid (a weak acid), a small amount of hydrogen ion, sodium ion, and bicarbonate ion (a strong base) derived from nearly all the sodium bicarbonate of which only a little remains undissociated. Its actual *p*H depends as usual on the ratio between the concentrations of base and acid.

On addition of hydrochloric acid, the H^+ ions of this acid nearly all combine with the bicarbonate ions to produce feebly dissociated carbonic acid so that the actual increase in acidity is only a small fraction of that which would be caused by the hydrochloric acid in water alone. Every bicarbonate ion removed is replaced by a chloride ion so that the total anion concentration is maintained unaltered and, as must necessarily be the case, cation-anion balance is maintained. The removal of H^+ can only proceed so long as bicarbonate ions remain ; in other words the neutralizing capacity (= buffer power) for acids is quantitatively limited by the concentration of the base.*

When a base is added to this buffer system a similar chemical action occurs and again the concentration of hydrogen ions is stabilized. Sodium hydroxide, for example, which is almost completely ionized in solution with liberation of the very strong base, hydroxyl ion, reacts with the carbonic acid forming water. More precisely, the OH^- combines with the free H^+ to produce water, and, the equilibrium, $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$, being disturbed, more carbonic acid dissociates, the process continuing until either the acid or the OH^- is completely used up. The effect is that, so long as the buffer system remains unexhausted, some carbonic acid has been converted to bicarbonate ions (enough to remove the hydroxyl ions as water) and the remainder is, as usual, slightly ionized so that the concentration of hydrogen ions is very little altered.

It is clear that in a solution containing several buffer systems they must be, and must always remain, in mutual equilibrium. If, therefore, the ratio of acid to base is known for any one of the systems the *p*H of the mixture is known. Since, in plasma, the bicarbonate-carbonic acid buffer is by far the most important quantitatively and also the easiest to measure, the total CO_2 content of plasma which is the sum of the $[HCO_3^-]$ and the relatively small $[H_2CO_3 + CO_2]$ is commonly taken to represent the total buffering capacity, and though this is not precisely true under all circumstances it is a good approximation for ordinary purposes.

*The buffering capacity with respect to acid is evidently the " available base reserve." It has often been termed the " alkali reserve," but this term is to be avoided since an alkali is really a soluble hydroxide.

THE *p*H-STABILIZING MECHANISMS OF BLOOD AND TISSUES

Haemoglobin has a special place in the *p*H-stabilizing mechanisms of blood because (*a*) haemoglobin and oxyhaemoglobin have different iso-electric points and different ionization constants so that at the *p*H of blood the liberation of oxygen from one gram molecule of oxyhaemoglobin involves the absorption of about 0.7 g. of hydrogen ion (and the release of an equivalent amount of potassium ion in exchange). The hydrogen ion is provided mainly by carbonic acid but could come from any acid which penetrates the red cells. (*b*) Haemoglobin, more easily than other proteins, reacts reversibly with carbonic acid to form a still weaker carbamino-acid; this specific contribution to the disposal of carbonic acid involves an increasing accumulation of carbamino-haemoglobin as the blood passes through the capillaries and a sharp reversal when, in the lungs, the equilibrium is disturbed, carbon dioxide being excreted, carbonic acid converted to carbon dioxide under the influence of carbonic anhydrase, and, consequently, carbamino-haemoglobin decomposed.

The existence of these two mechanisms, backed by the very efficient excretion of CO_2 in the lungs, ensures that, so long as the respiratory exchange is normal, extra metabolic production of CO_2 does not result in a disturbance of the acid-base ratio.

The buffers which are effective over the *p*H range of the blood and tissues consist of three systems: bicarbonate-carbonic acid, protein anion-protein, and monohydrogen phosphate-dihydrogen phosphate. Quantitatively, the bicarbonate-carbonic acid system is the most important in the plasma, but is much less so in the cells. These buffers must, for a given fluid, be in mutual equilibrium, and are in electrical neutrality by virtue of the cations, mainly sodium in the plasma and extracellular fluid, mainly potassium in the intracellular fluid. Since, however, the cell membranes are selectively permeable and transfer of ions into and out of the cells is partly governed by this and by the Donnan equilibrium, it is possible at times for the intracellular and extracellular fluids to get "out of step." There may, for example, be an abnormal diminution in the cell buffer capacity not immediately reflected in the plasma, with, as part of the complex movement of ions, a loss of potassium from the cells in exchange for hydrogen ions retained or taken in. This would constitute an "intracellular metabolic acidosis" which, if prolonged, would lead to potassium depletion.

EXCRETORY MECHANISMS

The concentration of the blood and tissue fluid buffers is continuously being maintained by the respiratory and renal mechanisms. The excretion of CO_2 by the lungs not only restores the special haemoglobin mechanisms for re-use, but is capable of adjusting the bicarbonate-carbonic acid system since the rate of excretion of the acid (after conversion to CO_2) depends upon the rate and depth of respiration. The kidneys function by excreting, selectively, acids and hydrogen ions or basic ions in such a way as to vary the urinary *p*H while maintaining the plasma *p*H as nearly constant as possible. Some very weak acids like uric acid are excreted as such, and, being largely undissociated, have little effect on *p*H. Hydrogen ions are excreted to a small extent in that form since normal urine is acid, but mainly in combination with base in the form of NH_4^+ and $H_2PO_4^-$. By this means much hydrogen ion can be removed from the body without a very high acidity being reached in the urine. At the same time, since these ions, excreted by the tubules, must be exchanged for metallic cations, the spent buffer salts are restored. For example, an acid HX is "neutralized" by the buffer systems including the system ($H_2CO_3 + Na^+ + HCO_3^-$), the products being ($Na^+ + X^-$ and H_2CO_3). The carbonic acid may be excreted as CO_2, but the Na^+ and X^- ions are filtered into the glomerular fluid. During the passage of this fluid through the tubules, NH_4^+ and HCO_3^- are produced in the tubular cells, the former from NH_3 (derived mainly from glutamine by enzymic hydrolysis to an extent controlled by the *p*H of the plasma) by combination with H^+ from H_2CO_3 (the end-product of oxidative metabolism). The ammonium ion is then exchanged for the sodium ion in the tubular fluid and, as a net result, $NH_4^+ + X^-$ are excreted in the urine, whilst the reabsorbed Na^+ and the HCO_3^- of the cells are passed back into the plasma, restoring the *status quo*. Similarly, H^+, secreted by the tubular cells, combines with $HPO_4^=$ to form $H_2PO_4^-$ and the Na^+ so released is reabsorbed to take its place.

Tubular lumen

$$Na^+ + Na^+ + HPO_4^= + H^+ \rightarrow Na^+ + H_2PO_4^-$$

$$\downarrow \qquad\qquad \uparrow$$

$$Na^+ \qquad\qquad H^+ + HCO_3^-$$

Tubular cell

The amount of H^+ which can be combined with phosphate in this way is, of course, limited

by the amount of phosphate available for excretion and this is not very great, some 40 mEq. per day; adjustment is by manipulation of the $H_2PO_4^-$: $HPO_4^=$ ratio rather than by change in the total phosphate excretion. The NH_4^+ mechanism is much more flexible because the amount of NH_4^+ obtainable is virtually unlimited; the ordinary excretion of ammonia, some 30–50 mEq./day, may be diminished almost to zero or increased as much as tenfold according to the need for buffer reconstitution.

ACIDOSIS AND ALKALOSIS

Acidosis may be defined as any condition in which the ratio of acid to base in the plasma is increased or in which the concentration of available base, i.e., the buffering power, is reduced. In the first of these situations the *p*H is reduced; the buffering power is not necessarily reduced and may even be above normal. In the second, the processes which produce a decreased buffering power *in vivo* must reduce the *p*H to some extent, but the fall is often so small as to be inappreciable.

Conversely, alkalosis consists of a decrease in the acid : base ratio or an increase in the buffering power.

It is convenient to classify acidosis and alkalosis as respiratory or metabolic. In the former, abnormality of the carbonic acid-bicarbonate system constitutes the primary fault and results from alterations in the CO_2 excretion caused by changes in the respiratory or circulatory mechanism. In the latter, such causes as metabolic over-production of acid, excessive ingestion of base, excessive loss of acid or base by abnormal routes, and failure of the renal excretory processes, alter the buffering power of the body fluids and possibly also the acid : base ratio.

COMPENSATION AND REPAIR

The existence of the homeostatic excretory mechanisms, which tend continuously to adjust the acid : base ratio and the buffering power of the plasma (and hence, by way of internal ion transfer, of the other body fluids), means that any movement towards acidosis or alkalosis automatically provokes a counter-movement. The control of the *p*H seems to be of supreme importance and the initial restorative changes are directed to this end. Frequently the acid : base ratio is returned towards normal (or is prevented from diverging from normal) at the expense of changes in the buffering capacity; a second abnormality is imposed on the first, and the process is one of compensation rather than repair. Thus a respiratory acidosis involving retention of carbonic acid would be repaired by an increased excretion of CO_2; the circumstances in which such an acidosis occurs, however, make such increased excretion difficult or impossible, and in fact the renal mechanisms compensate by raising the acid excretion and permitting an increase in the plasma and tissue buffer concentrations. The apparently anomalous situation thus arises of an acidosis with an increased plasma bicarbonate content; a respiratory acidosis has been compensated by the development of a superimposed metabolic alkalosis. Conversely, a respiratory alkalosis, involving reduction in the plasma H_2CO_3, is compensated by a decrease in the renal excretion of H^+, NH_4^+, and $H_2PO_4^-$ with increased excretion of HCO_3^-—and the corresponding amount of Na^+—with consequent decrease in the plasma [HCO_3^-]. Repair would involve the retention of H_2CO_3.

In a metabolic acidosis, with reduced plasma [HCO_3^-], i.e., reduced buffer capacity, compensation is rapidly initiated by an increased excretion of CO_2 provided the respiratory movements are not affected by some associated disease. True repair, however, involves the much slower adjustment, to whatever extent is possible, of the renal mechanism, with increased output of H^+, NH_4^+, and $H_2PO_4^-$ and the consequent increased reabsorption of Na^+ to allow rebuilding of the plasma concentration of bicarbonate and other buffer salts.

The occurrence of a metabolic alkalosis involves the reverse changes. Again compensation, consisting of the superimposition of increased [H_2CO_3] on the increased [HCO_3^-], is provided by changes in the respiratory movements with retention of CO_2. Again, also, the buffering power of the plasma as well as its *p*H can only be normalized if the kidney can decrease the excretion of H^+, NH_4^+, and $H_2PO_4^-$ allowing the urinary *p*H to rise, and increase the excretion of HCO_3^-, thus decreasing the abnormally high plasma [HCO_3^-]. The excretion of metallic cations like Na^+ will of course alter in harmony with these changes.

In practice compensatory and repair processes proceed simultaneously, their relative rates being determined by the relative efficiencies, in the particular circumstances, of the respiratory and renal mechanisms and by the fact that if both mechanisms are normal the former is the more rapid.

METHODS OF ASSESSING THE STATE OF THE ACID : BASE EQUILIBRIUM

It is clear that abnormalities of the *p*H regulating systems of the body can only be assessed fully by a multiplicity of measurements; there is no single parameter satisfactory in all cases. Moreover, intra- and extra-cellular fluids do not always move in mutual conformity with respect to their acid : base equilibrium, and, since measurements are feasible only in blood or plasma, it is sometimes necessary to infer intracellular abnormalities from indirect evidence.

Since *p*H, an expression of the ratio acid : base, and total buffering power, a function of the base concentration, can vary independently, it is necessary to know both. Quite small changes in *p*H can be very important and therefore only a very accurate *p*H meter can suffice; even with an adequate instrument careful control of temperature is essential, as also is protection against disturbance of the equilibrium by loss of CO_2 to the air. Nevertheless the direct measurement of *p*H is important and is really essential for the proper assessment of respiratory acidosis and alkalosis. Indirect methods of measuring *p*H on the basis, e.g., of determination of arterial plasma $[HCO_3^-]$ and pCO_2, the latter from analysis of the alveolar air with the assumption that its CO_2 content represents the arterial pCO_2, are theoretically possible but unsatisfactory in practice; indeed pCO_2, which is usually abnormal in respiratory disturbances, is best measured by calculation from *p*H and arterial $[HCO_3^-]$. Arterial blood, however, may be replaced by free-flowing capillary blood.

The total buffering power of the plasma could be measured by actual titration to some arbitrary end-point chosen as representing the physiological limit of adjustment. Usually, however, measurement is restricted to the bicarbonate system which, besides being quantitatively the most important in plasma, is the easiest to measure and is in equilibrium with the others. In practice measurement gives the sum of the concentrations of bicarbonate ions, carbonic acid, and dissolved CO_2, but, since the bicarbonate normally constitutes about 95% of this and never, even in extreme acidosis, falls below 90%, little error is involved in accepting "total CO_2 content" as equivalent to $[HCO_3^-]$. The normal range in venous blood is 24–32 mEq. HCO_3^- per litre (50–70 ml. CO_2 per 100 ml.). This measurement is made on venous blood (collected and centrifuged under oil).

For the investigation of acid : base disturbances known to be of metabolic origin with normal respiratory processes, measurement of plasma *p*H is of minor importance and it is determination of buffering power which gives valuable information. It is here that "CO_2-combining power" may profitably be substituted for "total CO_2 content." This is simply the assessment of buffering power by measuring $[HCO_3^-]$ (plus the relatively small $[H_2CO_3 + CO_2]$) in venous blood or plasma which, after withdrawal without precautions against loss of CO_2 to the air, has been re-equilibrated with an atmosphere containing 5.5% CO_2 to represent normal alveolar air. Normally, under these conditions, the re-equilibrated blood on addition of excess acid liberates 54–70 ml. CO_2 per 100 ml. blood; lower figures are found in metabolic acidosis and in compensated respiratory alkalosis, higher figures in metabolic alkalosis and compensated respiratory acidosis.

Investigation of acidosis and alkalosis may include measurement of urinary *p*H and titratable acidity and of urinary ammonia, but these, though occasionally of interest, are generally of minor importance. Cognizance should, however, be taken of the secondary changes in the plasma concentrations of sodium, potassium, and chloride, for these may be important in relation to treatment.

SECONDARY ELECTROLYTE CHANGES

Acidosis and alkalosis invariably consist of changes in the acid : base ratio or in the total buffering power or both. The complex ionic interchanges involved inevitably result in disturbances of those ions which are neither acids nor effective bases, principally Na^+, K^+, and Cl^-. Usually, although the exact mechanism is sometimes obscure, the plasma chloride is lowered, but occasionally, as after ureteral transplantation, acidosis is associated with hyperchloraemia. Sodium depletion may accompany, e.g., the acidosis due to excessive loss of HCO_3^- in severe diarrhoea, for anions cannot be lost without an equivalent loss of cation. Potassium depletion may be a result of intracellular acidosis, for if hydrogen ions produced in the cells are for some reason retained there and react with the buffer systems, an equivalent amount of K^+ leaves the cell and, with normal renal function, is excreted in the urine.

Widespread electrolyte changes and consequently widespread changes in water distribution and excretion must accompany the development and repair of acid : base abnormalities. On the other hand, acidosis and alkalosis may be the result of disturbances among the non-basic and non-acidic ions. One example is the hyper-

chloraemic acidosis mentioned above and another is the acidosis which results from various forms of potassium depletion. The first of these examples is discussed later. In the second, it has been suggested that K^+ and H^+ compete for the same excretory sites in the renal tubular cells and that, therefore, increased excretion of K^+ must lead to some retention of H^+ which, combining with available base, produces acidosis.

CLINICAL CONDITIONS ASSOCIATED WITH DISTURBANCES OF ACID : BASE EQUILIBRIUM

Serious disturbances of the acid : base ratio and of the buffering power are likely to arise in patients suffering from diseases of those organs which are responsible for the regulation of the reaction of the body fluids, namely the lungs and the kidneys. Since the effect of such diseases is usually to diminish the rate of excretion of metabolic end-products, they commonly result in acidosis. Disturbances of regulation can, however, also be caused by loss of alimentary tract secretions, as in vomiting, diarrhoea, or fistula, or by grossly abnormal production of metabolic intermediates, as in uncontrolled diabetes. Acid : base disturbances are also readily produced by the administration of drugs, some acting by virtue of their own chemical nature, e.g., sodium bicarbonate, and others through their action on excretory mechanisms, e.g., the more potent diuretic drugs. The simultaneous occurrence of more than one of these factors is particularly likely to give rise to a clinically recognizable disturbance, as, for example, the patient who vomits repeatedly due to pyloric stenosis but also attempts to relieve his discomfort by frequent ingestion of alkaline mixtures.

(1) Acid : Base Disturbance of Respiratory Type

Carbon Dioxide Retention.—The role of the lungs in acid : base regulation consists in the excretion of carbon dioxide at such a rate as to maintain the arterial CO_2 tension at around 40 mm. Hg, the rate and depth of respiration being regulated towards this end by centres in the brain-stem. Normally the partial pressure of CO_2 in arterial blood equals that in alveolar air, although discrepancies may occur if gases in the lungs are wrongly distributed, as, for example, in open-thorax operations or even in head-down postures.

Upper respiratory tract obstruction as a cause of respiratory acidosis is unusual except in comparatively acute forms, e.g., laryngospasm, inhaled foreign body, and the like, although accumulated bronchial secretions can have a similar effect.

Chronic respiratory acidosis can, however, be readily produced in a variety of ways by pulmonary disease. The patient may have less alveolar tissue than normal, as in emphysema, so that the surface area available for gas exchange is reduced. The residual air after normal expiration may also be considerably increased, so that the inspired air, even if of normal volume, is unable to reduce the alveolar CO_2 tension sufficiently, and in consequence the arterial pCO_2 is high.

Another factor is the elasticity of the lung tissue ; in pulmonary fibrosis, for example, there appears to be not only a diminution in alveolar ventilation, but also poor gas mixing due to lung rigidity preventing elastic recoil.

In pulmonary oedema, the accumulation of fluid reduces the volume of gas available for equilibration with the alveolar capillary blood. Impaired transport of carbon dioxide across the alveolar membrane does not appear to be a significant factor in this condition, since the high solubility of CO_2 permits adequate diffusion, even across an abnormally thick fluid film.

In all these states, therefore, the effect is a reduction in the rate of excretion of carbon dioxide, or, to be more precise, an increase in the gradient of CO_2 tension between blood and inspired air which is required in order to maintain excretion. Carbon dioxide excretion must balance the rate of production in the tissues, otherwise acute asphyxia quickly results, but the arterial CO_2 tension is a reliable index of incipient failure of excretion. There may not always be a demonstrable abnormality in acid : base ratio or in buffering capacity in the resting subject, but mild exertion, or increased tissue metabolism, as in fevers, may precipitate frank respiratory acidosis in patients with chronic pulmonary disease.

It is now becoming clear that in the absence of mechanical obstruction in the air passages, abnormalities of blood flow through the lungs, in relation to the rate of alveolar ventilation, may also produce elevated arterial pCO_2 levels. Over-perfusion of regions of lung, for example, even if the alveolar ventilation rate is normal, results in the return to the systemic circulation of blood with an abnormally high CO_2 tension. Conversely, under-perfusion of normally ventilated alveoli results in an apparent increase in the functional dead space of the lungs, so that the total excretion of carbon dioxide may

be inadequate despite apparently adequate respiratory rate and excursion. These somewhat paradoxical situations involving respiratory acidosis occur mainly in thoracic injuries and in open-thorax operations, and are encountered more often by the anaesthetist than by the general physician.

If the inspired air contains an increased percentage of carbon dioxide, the level at which it is significantly retained is related to the rate of CO_2 production in the body as well as to the composition of the inspired gas. Apart from failure of ventilation in mine-workings, work-rooms, and the like, concentrations of CO_2 in the inspired air sufficient to cause respiratory acidosis are seldom encountered except in faulty respirators and anaesthetic apparatus. Some degree of compensation for the high concentration of CO_2 in the alveoli can be attained if the rate and depth of respiration are increased, but obviously no degree of overventilation can achieve excretion against a reversed gradient.

In the presence of normal pulmonary excretory capacity, respiratory acidosis can occur if the sensitivity of the respiratory centres is reduced. Notorious amongst respiratory depressants are such drugs as morphine, the barbiturates, and many anaesthetic agents, but simple hypoxia, especially if prolonged, is also a potent agent in this respect.

Interference with the neuromuscular aspects of respiration can arise in such diseases as bulbar poliomyelitis and progressive muscular atrophy, and also in traumatic lesions affecting the thoracic cage. It may also be produced deliberately in anaesthesia by the use of muscle relaxant drugs such as tubocurarine, and in this latter case it is the responsibility of the anaesthetist to ensure that ventilation is sufficient to prevent the development of respiratory acidosis. Unfortunately there is no simple means of monitoring the arterial CO_2 tension throughout the period of action of the drug, but there is considerable evidence that the state of oxygenation is not a reliable guide to the adequacy or otherwise of controlled respiration. It is probably less harmful to overventilate rather than underventilate the lungs of a patient receiving curare. In the recovery period, when respiration, though spontaneous, tends to be slow and erratic, some degree of respiratory acidosis is almost invariable.

No single laboratory determination is satisfactory as a means of detecting respiratory acidosis and of assessing its severity. Measurement of the CO_2-combining power of venous blood can yield misleading results in this condition, while determinations of the CO_2 content of arterial blood, though informative as regards the buffering capacity, do not reveal the extent of any disturbance of the acid : base ratio. Full information can be obtained from a determination of the *p*H and CO_2 content of a sample of arterial blood collected anaerobically, or alternatively the CO_2 tension of arterial blood may be determined tonometrically and calculations made from this value and the arterial blood *p*H. A third procedure is that of Astrup, who determines the *p*H of whole blood, and of plasma collected anaerobically and then exposed to a gas mixture containing a known percentage of CO_2. From these determinations $[HCO_3^-]$ and $[H_2CO_3]$ can be calculated, or read directly from nomograms. It should be noted that these procedures call for highly accurate determinations of arterial blood *p*H, which in turn require suitable apparatus, including a temperature-controlled bath, preferably at the bedside. Determinations of *p*H made on ordinary laboratory blood samples are futile for this purpose.

Since respiratory acidosis is due to defective excretion of CO_2, compensation and repair cannot be achieved by respiratory means unless the cause is easily remediable. The accumulation of CO_2 causes an increase in the plasma $[H_2CO_3]$, without at first a corresponding increase in $[HCO_3^-]$, so that there is a slight fall in plasma *p*H. This change brings into play the renal mechanisms of compensation, including increased production of NH_4^+ from NH_3 derived from glutamine in the kidney cells. At the same time, hydrogen ion, derived from carbonic acid in the tubule cells, is exchanged for sodium ion in the tubule lumen. The HCO_3^- thus present in the tubule cells enters the plasma (along with the reabsorbed sodium), and it is this entry of base, in the form of bicarbonate ion, into the circulation which restores the acid : base ratio and so returns the plasma *p*H to normal. There is still, however, an abnormally high plasma bicarbonate concentration, and the kidney cannot achieve complete restoration to normal so long as the cause of the respiratory acidosis persists, i.e., its role is compensatory rather than reparative.

Excessive Loss of Carbon Dioxide.—If the rate of CO_2 excretion exceeds the rate of production in the tissues, the partial pressure of CO_2 in the alveolar air falls, with corresponding fall in the $[H_2CO_3]$ in arterial blood. Since the $[HCO_3^-]$ is not at first reduced, the acid : base ratio alters, with a slight increase in blood *p*H, i.e., a

respiratory alkalosis appears. This state of affairs can be rapidly produced by voluntary overbreathing, and since the renal processes of compensation and repair are comparatively slow, a few deep respirations can, in susceptible subjects, produce apnoea, tetany, and even unconsciousness. A similar picture is met clinically in hysteria or in malingerers, but is rarely seen as a manifestation of somatic disease. The rapid respirations of pneumonia do not result in alkalosis, since the respirations are shallow and total alveolar ventilation is, in fact, reduced. Controlled respiration which is too deep or too rapid, as can arise in a poliomyelitis patient treated in a respirator, also results in respiratory alkalosis, since the compensatory mechanism of apnoea is inoperative.

Processes of renal compensation and repair in prolonged respiratory alkalosis are achieved, as one would expect, by the excretion of a neutral or alkaline urine containing an increased concentration of bicarbonate, while the excretion of H^+ as NH_4^+ and $H_2PO_4^-$ is minimized. Changes in the blood in respiratory alkalosis may not be readily detected except by a sensitive *p*H meter, since only a comparatively small reduction in $[H_2CO_3]$ may be present, and determinations of CO_2 content and CO_2-combining power may give results within the normal range, or may be low as the result of compensation.

The principal changes found in the plasma anions in respiratory acidosis and alkalosis are summarized in Fig. 1.

(2) Acid : Base Disturbances of Metabolic Type

Metabolic Acidosis from Excessive Production of Acids.—The processes of normal metabolism result in the production of acidic substances which, if unbuffered in the cells and in the body fluids, would result in intolerably acid conditions. In addition to carbon dioxide (which though quantitatively the most important is, as we have seen, unable to cause acidosis unless excretion is impaired) several other acids are produced as end-products of metabolism, including sulphuric and phosphoric acids. In addition to these end-products, however, there is a considerable number of metabolic intermediates, normally present in small amounts only, and rapidly degraded and re-formed in the course of cell metabolism. This group includes such substances as lactic, pyruvic, citric, and acetoacetic acids, which do not ordinarily enter the extracellular fluid in amounts sufficient to influence acid : base balance directly. One exception is, of course, lactic acid, which

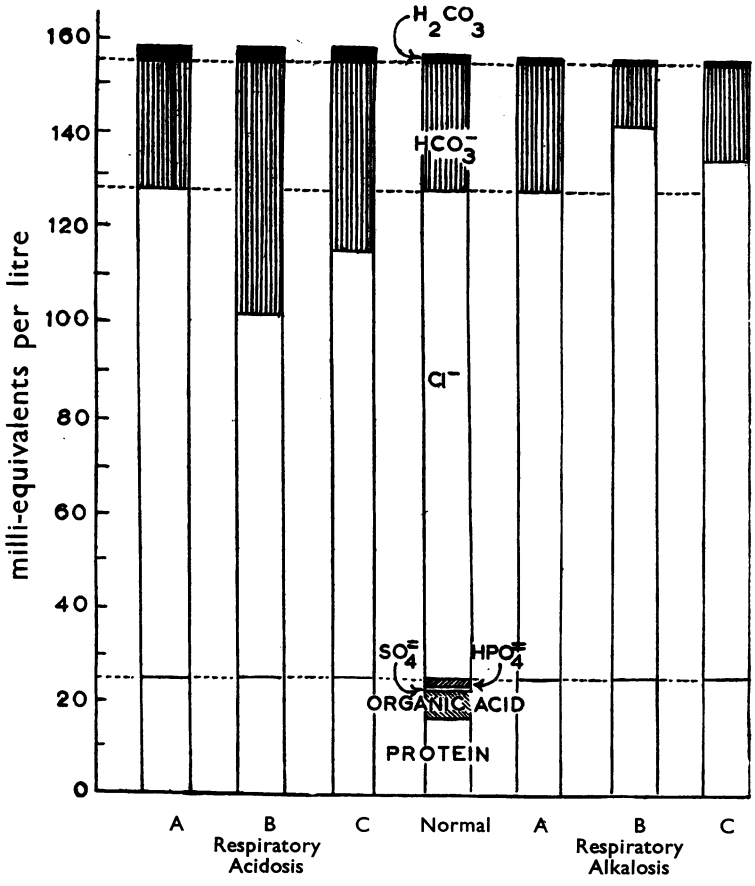

FIG. 1.—Plasma anion changes in respiratory acidosis and alkalosis. In each case, column A shows the anion composition of the plasma characteristic of the primary abnormality ; column B shows the composition when compensation is complete, i.e., the $[HCO_3^-]/[H_2CO_3]$ ratio is restored to normal ; column C shows the composition, with partial compensation, usually found.

accumulates sufficiently during severe muscular exercise to require buffering in the body fluids as well as within the muscle cells.

If, however, there is a metabolic block which results in excessive production of one or more of such acids, or in failure of utilization, the buffering capacity may be exceeded and clinically recognizable metabolic acidosis appears.

The commonest clinical cause of severe metabolic acidosis is uncontrolled diabetes mellitus, in which, owing to impaired carbohydrate utilization in the tissues, there is increased mobilization and partial oxidation of depot and tissue fat. This augments the production in the liver of acetoacetic and β-hydroxybutyric acids, and, owing in part at least to the reduced ability of the peripheral tissues to oxidize such acids to readily disposable CO_2, they accumulate in body fluids. The immediate buffering minimizes the fall in *p*H, and, although there is a resulting increase in $[H_2CO_3]$, this is removed by increased rate and depth of respiration so that the normal acid : base ratio is restored with, however, a lower bicarbonate concentration in the plasma, demonstrable as a reduced CO_2-combining power. Continuing over-production of acids also leads to renal compensation and repair, by increased excretion of hydrogen ion, mainly in combined form as NH_4^+ and $H_2PO_4^-$, and with increased acidity of the urine. There is at the same time an increased urinary loss of sodium, chloride, and water, but these do not directly influence the acid : base disturbance.

In diabetic coma, the plasma electrolyte pattern is as shown in Fig. 2. The arterial blood *p*H is often in the region 7.1–7.3, and the plasma bicarbonate concentration may fall to between 10 and 15 milliequivalents per litre.

A similar, but less severe, metabolic acidosis may be produced by starvation, with increased utilization of body fat. It may also arise from carbohydrate deficiency produced by excessive removal of blood glucose, as in glycogen storage disease.

Metabolic Acidosis from Ingestion of Drugs.—There are a few drugs which, though themselves neutral salts, cause, on oral administration, acidosis of metabolic type. Of these, the best known, and clinically the most useful, is ammonium chloride, but the mechanism whereby acidosis is produced is not at first obvious. Admittedly NH_4^+ is an acid, though a weak one, but since it does not give rise to hydrogen ions at body *p*H, it could not produce acidosis directly. The explanation of its effect lies in the conversion of ammonium ions to urea in the liver, which involves the withdrawal of two HCO_3^- ions from the plasma, and the production of one H_2CO_3 molecule for every molecule of urea formed. The reaction, in greatly simplified form, may be represented as follows:

$$2\,NH_4Cl + 2\,\underset{\text{(from plasma)}}{HCO_3^-} \rightarrow \underset{\text{Urea}}{(NH_2)_2CO} + H_2CO_3 + 2\,Cl^- + 2\,H_2O$$

It is thus seen that ammonium chloride produces a reduction in plasma $[HCO_3^-]$ and an increase in $[H_2CO_3]$. There is also an increase in plasma

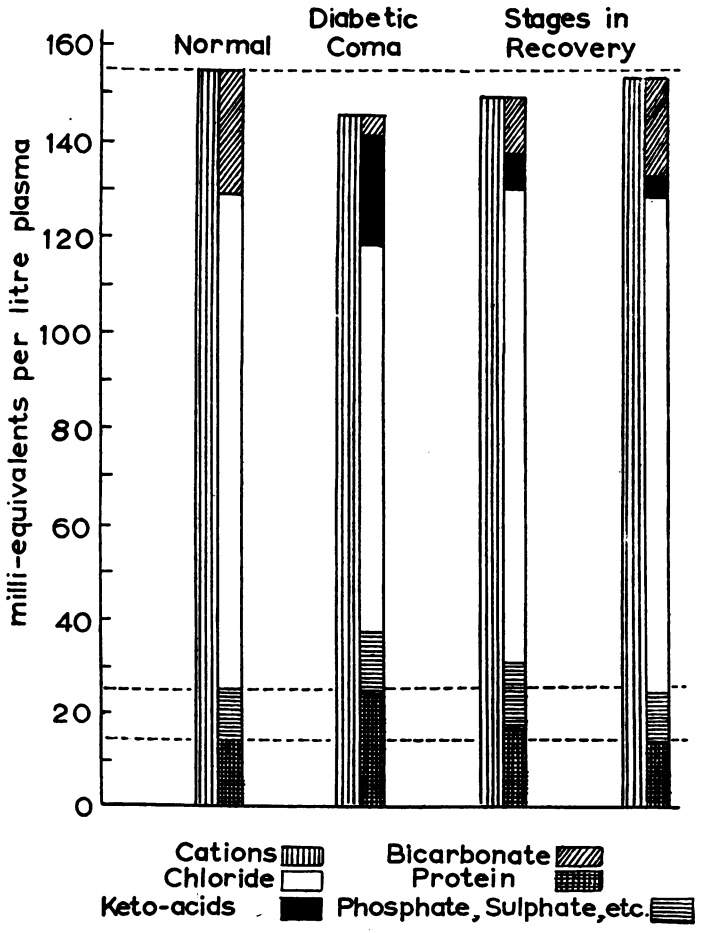

FIG. 2.—Plasma anions in diabetic coma and during recovery.

[Cl^-], but this is a side effect and not a fundamental part of the acidosis. There is no change in osmotic relationships and plasma [Na^+] is not affected.

Metabolic Acidosis Resulting from Failure of Excretion.—Since in normal metabolism acids were continually being produced, failure to excrete a sufficiently acid urine must result in accumulation of H^+ in body fluids. Reconstitution of the buffering capacity cannot be achieved by the lungs, and other routes of excretion (skin, alimentary tract) are insignificant for this purpose.

The acidosis of renal insufficiency has at least two origins. Probably the more important is a diminished production of NH_4^+ in the tubule cells (from glutamine and H_2CO_3), and therefore there is less excretion of hydrogen ion in the form of ammonium ion, as well as less HCO_3^- returned to the plasma to reconstitute the bicarbonate buffer and restore the acid: base ratio. Secondly, there is reduced urinary excretion of phosphate ions, associated therefore with diminished tubular capacity for exchange of H^+ for Na^+, in the conversion of Na_2HPO_4 to NaH_2PO_4 which accompanies tubular acidification of the urine. It is not clear whether the reduced phosphate clearance in renal failure is of glomerular origin, or is secondary to some factor as yet unknown. A further consequence of failure to exchange H^+ for Na^+ is an increased urinary loss of sodium, but this is incidental to, and not part of, the acidosis.

The plasma of a patient in renal failure will therefore show a reduction in [HCO_3^-], normal [H_2CO_3], normal or low [Cl^-], and a characteristic increase in inorganic phosphate concentration.

A special case of partial failure of excretion occurs in patients whose ureters have been transplanted into the lower alimentary canal, and in whom, therefore, reabsorption of urinary constituents can take place. Such patients frequently develop metabolic acidosis which is characteristically associated with diminished plasma [HCO_3^-] but elevated [Cl^-], phosphate and sulphate. Plasma sodium concentrations are normal. This unusual hyperchloraemic pattern does not arise if the urine is not allowed to accumulate in the colon, and isotopic studies have shown that, while both Na^+ and Cl^- are readily absorbed from the colon, the absorption of chloride ion is considerably more rapid. Since an anion cannot be transported without cation, one must either postulate that the absorption of chloride involves an exchange mechanism, with equivalent excretion of another anion, most probably HCO_3^-, or else that a cation other than sodium or potassium, most probably NH_4^+, is also absorbed. The former seems the more likely mechanism, but either process would result in metabolic acidosis by the mechanisms described earlier.

Oral administration of sodium bicarbonate restores normal plasma anion concentrations, and this finding is consistent with either mechanism. In the former case it would act by restoring the plasma [HCO_3^-], and in the latter by acting, via the renal glutamine mechanism, to reduce the urinary excretion of NH_4^+. In both cases, the administered sodium would be excreted along with the surplus chloride, and such patients would not develop oedema from salt retention.

It should be emphasized that the acidosis is not primarily created by the abnormal reabsorption of chloride ion but is produced secondarily by the other ionic transfers which accompany it.

Metabolic Acidosis Resulting from Abnormal Loss of Base.—Direct loss of intestinal secretions, either through prolonged diarrhoea, or from an intestinal fistula, results in loss of HCO_3^- along with equivalent amounts of metallic cations and a certain amount of chloride. Although such losses of Na^+, K^+, and Cl^- cause considerable water and electrolyte depletion, with reduction in the extracellular fluid volume, only the loss of HCO_3^- is responsible for the acid: base disturbance. Once again the plasma pattern shows a reduction in [HCO_3^-], while compensation via the lungs reduces the [H_2CO_3] so that the acid: base ratio is restored at a lower level of bicarbonate buffer concentration. Renal compensation and repair involve, as in other examples of metabolic acidosis, the production of an acid urine having a high concentration of NH_4^+, and an increased excretion of H^+ in the form of $H_2PO_4^-$.

Metabolic acidosis due to increased loss of bicarbonate occurs during the administration of certain diuretic drugs, notably chlorothiazide. The urine, during the diuresis, contains increased amounts of Na^+, K^+, Cl^-, and HCO_3^-, while the urinary *p*H, ordinarily around 5.0–6.0, rises to about 7.5–7.9. Chlorothiazide is a carbonic anhydrase inhibitor *in vitro*, and therefore might be expected to reduce, *in vivo*, the amount of H^+ formed from $CO_2 + H_2O$ in the tubule cells and available for exchange with Na^+ in the tubule lumen. In consequence, the amount of H_2CO_3 entering the blood from the kidney cells would

be greater than normal, while the amount of HCO_3^- entering the plasma would be reduced. It is not yet agreed, however, to what extent the effects of chlorothiazide are attributable solely to its action on carbonic anhydrase activity.

Metabolic Alkalosis Resulting from Excessive Intake of Base. — Antacid drugs used in the treatment of dyspepsia act initially by neutralization of gastric HCl, thereby preventing the subsequent interaction of HCl with $NaHCO_3$ in the intestinal secretions. In consequence, the HCO_3^- of the intestinal secretions is reabsorbed where normally much of it is converted to H_2CO_3 in the gut. If a drug such as sodium bicarbonate is taken in amounts greater than can react with the HCl secreted, there is, in addition, absorption of the HCO_3^- of the drug itself. The plasma $[HCO_3^-]$ is increased, and both CO_2 content and CO_2-combining power are high.

Two restorative processes are possible, respiratory and renal. In the former, the rising blood *p*H reduces the activity of the respiratory centres and the rate and depth of respiration are reduced. Thus the acid : base ratio is restored through an increase in the plasma $[H_2CO_3]$, but at a higher level of buffering capacity than normal. The renal repair processes include diminished NH_4^+ production, diminished exchange of H^+ and Na^+ in the tubules, and increased glomerular filtration of HCO_3^-, the overall result being an increase in urinary *p*H and a reduction of plasma $[HCO_3^-]$.

A metabolic alkalosis may be produced, or an existing metabolic acidosis corrected, by the oral or parenteral administration of certain sodium or potassium salts of weak organic acids. Important examples are lactates and citrates, and for such salts to produce alkalosis it is necessary for the anions to undergo metabolic oxidation in the cells, with the production of carbonic acid. The complete oxidation of one molecule of sodium lactate produces two molecules of carbonic acid and one bicarbonate ion, held in electrical neutrality by the sodium ion of the original lactate. Since the H_2CO_3 can be disposed of by the lungs, the effect is the same as that produced by administration of sodium bicarbonate.

It must again be emphasized that the alkalosis-producing effect of these salts is derived from the strong base HCO_3^- produced by their metabolism, and not from the cation which they provide. The latter may of course be valuable if there is simultaneous sodium depletion, but it does not directly affect the acid : base disturbance.

Metabolic Alkalosis Produced by Loss of Gastric Secretions.—Loss of HCl, as in vomiting or in aspiration of upper alimentary tract secretions, results in metabolic alkalosis, which may be severe if the loss is prolonged. The blood leaving the gastric mucosa during active HCl

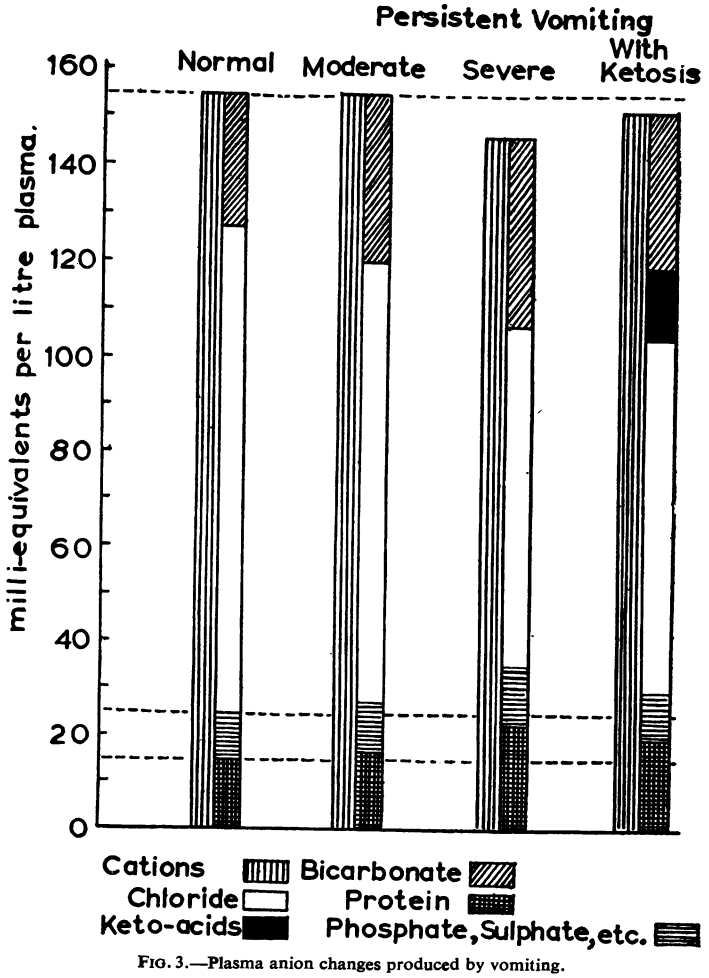

FIG. 3.—Plasma anion changes produced by vomiting.

secretion has a high [HCO_3^-] and low [H_2CO_3], i.e., a temporary metabolic alkalosis occurs which results in transient secretion of alkaline urine following a meal. In the prolonged vomiting of, say, pyloric stenosis, a somewhat similar condition persists, but with progressive diminution in plasma [Cl^-] which is replaced by HCO_3^-. The plasma changes are summarized in Fig. 3. Respiratory compensation through reduced CO_2 excretion is not particularly effective, but the tendency to apnoea may help in the bedside assessment of the severity of the alkalosis. Urinary changes are similar to those which follow administration of bicarbonate, but quantitative measurement of the degree of disturbance can best be made by determination of the plasma [HCO_3^-]. In this context, the determination of the CO_2-combining power of venous blood is all that is necessary, and is preferable to chloride determinations as being a more consistent index of early changes.

Patients suffering from prolonged vomiting usually take an inadequate amount of food, and in consequence tend to increase the breakdown of tissue fat with the production of "starvation ketosis." This condition is, by itself, a cause of metabolic acidosis, and therefore its occurrence in association with severe vomiting may lead to a somewhat confusing plasma anion pattern characterized by normal [HCO_3^-] but low [Cl^-], the deficit being made up by organic anions as shown in Fig. 3. It is thus possible for a patient to be in alkalosis and ketosis simultaneously, and correction of the ketosis, e.g., by parenteral administration of glucose, will commonly reveal the plasma anion pattern characteristic of metabolic alkalosis.

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SELECTED REFERENCES FOR FURTHER READING

(Since the paper describes the application of a particular viewpoint to established facts, a full bibliography is considered unnecessary.)

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