CLINICAL PATHOLOGY IN GENERAL PRACTICE

INTERPRETATION OF ELECTROLYTE CHANGES IN THE BLOOD

BY

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The general practitioner does not very often have to ask the laboratory for estimations of electrolytes; the results of such tests do come to him, however, in the letters about patients who have left hospital; and he himself may want to follow the electrolyte changes in some of the more chronic diseases he meets. This article sets out to recall the meaning of some of the chemical data that may be encountered and to indicate when the determinations may be useful. The treatment of acute disturbances of water and electrolyte balance was fully discussed by Dr. D. A. K. Black* in another Refresher Course. Disturbances in calcium and phosphorus metabolism, which are not closely related to water balance, are not discussed here.

The Body Fluids

The constituents of the body, other than those of the bones and fat, are held in solution in water. This water accounts for 50–60% of the weight of a man, depending on how fat he may be. One-third of this water is outside the cells in the tissues and in the blood; this is the extracellular fluid (E.C.F.). The remaining water, two-thirds of the total, is intracellular fluid (I.C.F.). The electrolyte content of the two fluids is quite different. In the extracellular fluid, sodium (Na^+) is the main cation; chloride (Cl^-) and bicarbonate (HCO_3^-) are the main anions. In the intracellular fluid of muscle, which accounts for most of the intracellular fluid, potassium (K^+) and magnesium (Mg^{++}) are the main cations; organic compounds of phosphorus are among the main anions. In both extracellular and intracellular fluid protein also acts as an anion, and this may be more important in the intracellular fluid, which contains the greater amount of protein.

The following principles govern the composition of the body fluids. The number of anions equals the number of cations. The reaction, or pH, depends on the concentration of hydrogen ions (H^+), but this concentration is very small compared with the concentrations of the other cations. The total concentrations of ions (cations+anions) largely determines the osmotic pressure of the solution. Changes in the reaction or in the osmotic pressure of the body fluids are usually rapidly compensated; for instance, a loss of base is likely to be accompanied by a loss of acid, and a loss of salt is accompanied by a loss of water.

Only the extracellular fluid can be sampled clinically. This is done when we collect and analyse the plasma or serum of the blood, although these do differ from the extracellular fluid outside the blood vessels in having a higher concentration of protein. Our knowledge of changes in the intracellular fluid is usually only inferred from changes in the serum. The sodium, chloride, bicarbonate, and potassium are the ions commonly measured.

Sampling

Blood is drawn from a vein with a clean, dry, sterile syringe, with a minimum of venous stasis; a wide-bore needle is better than a very fine one. The syringe may be lubricated with liquid paraffin. Instead of a syringe

many prefer a needle with a short length of rubber tubing attached to it through which the blood is allowed to flow. The blood is collected into a centrifuge tube or a screw-capped bottle. If the tube or bottle contains an anticoagulant the blood can be centrifuged and the plasma taken off without delay; this may take up less time than waiting for a clot to form and retract so that the serum separates. Oxalate is a convenient and cheap anticoagulant, but potassium and ammonium oxalates interfere with the determination of potassium and urea. Heparin (2 drops of 1:1,000 solution) does not interfere with these determinations, but it is more expensive. Plasma is needed for the determination of bicarbonate and chloride. Ideally it should be separated from blood which has been collected under a thin layer of liquid paraffin; this is to prevent contact with air and loss of CO_2 by diffusion. Plasma can also be used for determining sodium and potassium, but some laboratories prefer serum separated from blood without an anticoagulant. Serum or plasma for the determination of potassium must be separated as soon as possible because potassium leaves the red cells and gives a falsely high reading in the serum. For the same reason there must also be no haemolysis. The following contribute to haemolysis: traces of water, alcohol, or ether; vigorous expulsion of the blood into the tube, especially through a fine needle; excessive shaking and frothing. Haemolysed blood will not do for measuring the potassium or, incidentally, the phosphate.

The Units of Measurement

Concentrations of electrolytes may be expressed in milligrams per 100 ml. or in milli-equivalents per litre. The latter expression is the more natural, for analytical methods depend upon chemical equivalence, but some laboratories calculate their results in milligrams per cent. For example, they give the sodium and the chloride in the plasma as so many milligrams per 100 ml., and the CO_2 as so many volumes or millilitres per 100 ml. But concentrations of sodium and chloride cannot be exactly compared if they are expressed like this, because a milligram of sodium is not chemically equivalent to a millilitre of CO_2 or to a milligram of chloride. If we wish to make a sum of the anions to compare with the cations, we cannot add milligrams of chloride to millilitres of CO_2 . Many people now prefer to use units based on chemical equivalents. For example, equivalent weights of sodium, chloride, and hydrogen are 23 g., 35.5 g., and 1 g. These are also the atomic weights, in grammes, of these elements. Each one of these weights is 1 unit, which is defined as the weight which will combine with—or displace—1 g. of hydrogen. In hydrochloric acid, 35.5 g. of Cl is combined with 1 g. of H to produce the equivalent weight of HCl—namely, 36.5 g. Similarly, in sodium chloride (NaCl), 23 g. of Na combines with 35.5 g. of Cl to give the equivalent weight of the salt of 58.5 g. The equivalent weight of a substance dissolved in a litre of water makes a normal solution.

The unit usually employed in clinical work is one-thousandth of an equivalent weight, or a milli-equivalent (cf. milligram, millilitre). A milli-equivalent of any substance is the amount contained in 1 ml. of its normal solution. For monovalent elements a milli-equivalent is the atomic weight in milligrams, but the atomic weight of a divalent compound makes two equivalents, so that a milli-equivalent of, say, calcium is the atomic weight in

**British Medical Journal*, 1950, 1, 893. *Ibid.*, 1951, 2, 1207.

milligrams divided by 2. In practice, however, only Na, Cl, CO₂, and K are usually measured in milli-equivalents. A milli-equivalent of CO₂ is the molecular weight in milligrams; the volume occupied by this amount under standard conditions of temperature and pressure is 22.4 ml., so divide by 22.4 to convert millilitres of CO₂ to milli-equivalents. The figure for CO₂ in milli-equivalents is also the amount of bicarbonate, HCO₃⁻, that it can form. Note that :

The following Table shows the relation between cations and anions in normal plasma.

Base	mEq/litre	Acid	mEq/litre
Na ⁺	142	Cl ⁻	103
K ⁺	5	HCO ₃ ⁻	28
Ca ⁺⁺	5	Protein	16
Mg ⁺⁺	3	Organic acids	5
		HPO ₄ ⁻	2
		SO ₄ ⁻	1
Total 155		Total 155	

Isotonic saline (0.9%) contains 154 mEq per litre of NaCl. Although it is often called, physiologically, "normal saline," it is one-sixth the strength of a normal solution in chemical terms.

Changes in total base are accompanied by changes in total acid. Any major change in total base can only come from a change in Na⁺; and changes in total acid are largely changes in Cl⁻ and HCO₃⁻. The sum of cations and anions can remain equal in spite of rapid changes in either, because there is an unlimited supply of HCO₃⁻ from the CO₂ of metabolic processes to make up the balance when required, and any excess is promptly excreted by the lungs as CO₂. The amount of the bicarbonate depends simply on the excess of cations over the other, fixed, anions.

Normal values in milligrams and volumes per 100 ml. are shown for convenience :

Sodium	325-350 mg.
Chloride (as NaCl)	560-620 mg.
(as Cl)	340-370 mg.
CO ₂ combining power	55-75 ml.
Potassium	16-20 mg.

The following discussion assumes, however, that all values are expressed so that their chemical equivalence is obvious—that is, in milli-equivalents.

Changes in Na⁺ and Cl⁻ and the Accompanying Changes in HCO₃⁻

In conjunction with the clinical history, the levels of Na⁺ and Cl⁻ in the blood give information on the body stores of these ions. The changes in HCO₃⁻ (bicarbonate) which depend on these levels are also discussed here. Changes in acid-base balance are then described, followed by the changes in potassium (K), which is primarily an intracellular cation.

The serum sodium concentration can nowadays be estimated quickly and easily if a reliable flame photometer is available. In general, the concentration of sodium in the serum depends on two things at least: the amount of sodium and the amount of water in the extracellular compartment of the body fluids. A gain or loss in the amount of sodium leads at first to a proportionate gain or loss of water, so that a normal concentration of sodium, and hence a normal osmotic pressure, is maintained. It is only with the more severe disturbances that the serum values become abnormal.

Sodium depletion is the commonest electrolyte disturbance. Abnormal losses are usually from the gastro-intestinal tract, by diarrhoea and vomiting, and through the aspiration or the fistulous discharge of intestinal secretions. Abnormal renal losses of sodium occur in rarer conditions like Addison's disease and salt-losing nephritis, in which a low serum sodium is accompanied by the continued loss of sodium in the urine. In addition, low values for the serum sodium are quite often found in patients with oedema or

ascites who have taken a diet low in salt for a long time. Mercurial diuretics, often essential to the treatment, are partly responsible for this complication. They act by increasing the renal excretion of sodium and chloride, and if this does not lead to the desired mobilizing of oedema fluid the concentration of sodium in the body falls. The resulting deficit of sodium may, itself, make the patient ill, and if the serum sodium is low the proper treatment is to restore salt in spite of the risk that oedema may then be aggravated. Occasionally low values for the serum sodium concentration are the result not of a fall in the amount of sodium but of an increase in the amount of water in the extracellular compartment of the body fluids. Low values from dilution with water are observed when the osmotic pressure outside the cells is high compared with that within them; this may happen, for instance, with the hyperglycaemia of diabetes.

A high serum sodium nearly always means a lack of water, and the conscious patient will complain of thirst.

Changes in the plasma chloride are not always the result of abnormal gains or losses of chloride. Usually they depend on the changes in the sodium stores of the body or on changes in the acid-base balance. The plasma chloride may rise if an excess of chloride is given, as in ammonium chloride acidosis, or if the renal excretion of chloride is impaired. It may fall if chloride is lost by vomiting. In general, however, the chloride ion in the plasma is but a partner to the sodium; and the bicarbonate ion a passive make-weight in the anion column. The sum of the chloride and bicarbonate (in milli-equivalents) is a guide to the level of the sodium, which is normally some 15 mEq more than these two together. Organic acids in the plasma account for part of the difference between the values for Na⁺ and Cl⁻ + HCO₃⁻. When, for example, in diabetic ketosis the organic acids accumulate in abnormal amounts, the Cl⁻ and the HCO₃⁻ fall and the difference between the determined anions and cations is much increased. The mechanism of the acidosis that accompanies these changes is now considered.

Disturbances in Acid-Base Balance

An explanation of the relation between the CO₂ and the pH of the plasma necessitates a physiological digression. The reaction of the blood is maintained near a pH of 7.4, just on the alkaline side of neutrality. Two types of disturbance may upset it. One is respiratory, the other "metabolic." Both change the plasma CO₂, but for a given change in the pH they change the plasma CO₂ in opposite directions. This has sometimes led to confusion, but it is easily explained.

The CO₂ in the plasma is mostly that which is combined by base as bicarbonate. A small amount in solution forms the carbonic acid. The reaction, or pH, of the plasma depends on the ratio of the concentration of bicarbonate to carbonic acid :

$$pH = 6.1 + \log \frac{[\text{NaHCO}_3]}{[\text{H}_2\text{CO}_3]}$$

(The square brackets mean "concentration of,"). The bicarbonate is normally 20 times the carbonic acid :

$$pH = 6.1 + \log 20 = 6.1 + 1.3 = 7.4$$

Now it is clear that the pH may vary because of a change in [NaHCO₃] or because of a change in [H₂CO₃], but the effects of these changes will be opposite. Moreover, changes in the one can be compensated by changes in the other. The amount of H₂CO₃ in the plasma depends on the rate at which the lungs get rid of the CO₂ which the body produces. The amount of NaHCO₃ depends on the amount of sodium ions, Na⁺, not combined with other anions and free to bind bicarbonate.

Respiratory Disturbances

These disturbances depend on changes in the elimination of CO₂ from the lungs and hence on the concentration of carbonic acid in the plasma.

Alkalosis.—This results from the washing out of CO_2 from the blood—for example, in hysterical hyperventilation. The denominator of the fraction $\frac{[\text{NaHCO}_3]}{[\text{H}_2\text{CO}_3]}$ is diminished and the pH rises. To compensate for this the kidneys excrete sodium as bicarbonate and so restore the pH towards normal. The urine is therefore *alkaline*. The total plasma CO_2 is *low*.

Acidosis.—This results from a failure to eliminate CO_2 as may happen in advanced emphysema, in narcotic poisoning, and with laryngeal obstruction. The $[\text{H}_2\text{CO}_3]$ increases and the pH falls. In compensating, the kidneys conserve sodium bicarbonate and the urine is *acid*. The total plasma CO_2 is *high*.

"Metabolic" Disturbances

These disturbances depend on the amount of sodium that is free to combine with bicarbonate in the plasma.

Alkalosis.—This is the result of an increase in NaHCO_3 . An excessive intake of alkali can produce it, but a more usual cause is the loss of Cl^- from the stomach by prolonged vomiting as in pyloric stenosis. An excessive renal loss of Cl^- may be produced by treatment with mercurial diuretics. The resulting fall in plasma Cl^- frees Na^+ to combine with more CO_2 as bicarbonate. The rise in NaHCO_3 , leading to a rise in the pH of the plasma, depresses the respiratory centre and there is a rise in H_2CO_3 —that is, the metabolic alkalosis is so far as possible compensated by a respiratory acidosis. The kidneys excrete bicarbonate, and the urine is *alkaline*, unless there is also a deficit of Na^+ so severe that this compensation cannot take place. The total plasma CO_2 is *high*.

Acidosis.—This is a result of a fall in NaHCO_3 . This happens when acids stronger than carbonic acid accumulate in the blood and displace HCO_3^- from combination with Na^+ . Such acids are produced in diabetic ketosis. When an acidosis is produced therapeutically with NH_4Cl as an adjunct to mercurial therapy, the Cl^- ion accumulates and depresses the level of HCO_3^- . The fall in $[\text{NaHCO}_3]$ may also result from the direct loss of it. This is what happens in the acidosis of chronic diarrhoea. But, however caused, a metabolic acidosis is accompanied by an increased elimination of CO_2 from the lungs because a fall in the pH of the plasma stimulates the respiratory centre. The resulting fall in $[\text{H}_2\text{CO}_3]$ in the plasma compensates for the fall in $[\text{NaHCO}_3]$. The kidneys conserve base and excrete chloride, and the urine is *acid*. The total plasma CO_2 is *low*. In "renal acidosis" the kidneys are unable to excrete acid in the normal way and the urine remains *alkaline*, while acids accumulate in the body and produce an acidosis, with a low plasma CO_2 . This is an exception to the rule that with an acidosis the urine is acid and with an alkalosis it is alkaline. In general this rule does enable one correctly to interpret the changes in the plasma CO_2 which are opposite for respiratory and metabolic disturbances.

I may summarize by showing in tabular form the meaning of a rise or a fall in the plasma CO_2 .

Plasma CO_2	Reaction of Urine	Abnormality
High	Acid Alkaline	Respiratory acidosis Metabolic alkalosis
Low	Alkaline Acid*	Respiratory alkalosis Metabolic acidosis

* Except in "renal acidosis."

The metabolic disturbances in acid-base balance are more commonly observed than the respiratory; but either type of change compensates the other. For instance, a metabolic acidosis is compensated by over-breathing, which by itself would produce a respiratory alkalosis. The respiratory compensation is an emergency stop-gap: the metabolic disturbance is, in the end, corrected by the renal adjustments, and this requires that the stores and supplies of sodium and water be normal, so that the kidneys may function normally.

Changes in the Serum Potassium

The changes in the composition of the plasma considered up till now have concerned changes in the extracellular compartment of the body fluids. Potassium is the only intracellular ion to be discussed.

It is only in the last six years or so that it has become widely recognized that deficits of potassium at least as large as those of sodium are quite common; they mostly arise, as do the sodium deficits, from gastro-intestinal losses. It is occasionally necessary to follow the level of the serum potassium in renal disease and during treatment with adrenal hormones which produce an increased urinary excretion of potassium. The level of the serum potassium depends on three major factors: (1) the stores of potassium in the body, so that, on the whole, a low serum potassium (less than 3.5 mEq per litre) means that the stores are low; (2) the acid-base balance, for in the presence of an acidosis the serum potassium is often maintained at the normal level in spite of a cellular deficit of the ion; and (3) the function of the kidney; the renal excretion of potassium is not so delicately adjusted to the needs of the body as the excretion of sodium. The excretion may fail in nephritis and in oliguria, although there is an excess of potassium in the body, and the excretion of potassium may persist in the face of a deficit.

The finding of a low level of potassium in the serum means that there is a deficit of the ion, but the extent of the deficit cannot be ascertained, since it falls almost entirely upon the intracellular compartment of the body fluids. Only severe deficits seem to produce any symptoms.

Conclusion

Problems of electrolyte metabolism often obtrude themselves after therapy with artificial fluids, after operations and during acute illnesses. But they may also arise insidiously in more chronic diseases, and, although their recognition may be a signal for the patient to enter hospital, in many instances these disturbances can be prevented from becoming serious by attention to the diet and to the intake of water and of salts. But the diagnosis must precede treatment, and for this some chemical determinations and their proper interpretation may be unavoidable. The subject is a large one and this article has attempted no more than to point the way.

Next article on Clinical Pathology.—"Laboratory Control of Chemotherapy," by Professor Robert Knox.

THE MEDICAL CURRICULUM

REPORT OF THE UNDERGRADUATE EDUCATION COMMITTEE OF THE FIRST COUNCIL OF THE COLLEGE OF GENERAL PRACTITIONERS

"The hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course, ending only with death, for which the work of a few years under teachers is but a preparation."

WILLIAM OSLER, *The Student Life*.

The medical curriculum was discussed at the First World Conference on Medical Education organized by the World Medical Association in 1953, at which many original views were expressed and new experiments in medical education described.¹ The British Medical Association has devoted considerable attention to this subject^{2,3}; and the creation of the College of General Practitioners is in some part due to a revived interest in, and growing dissatisfaction with, the undergraduate and postgraduate training of family doctors.⁴ In the