THEORETICAL ASPECTS OF ACIDOSIS.

BY DUNCAN SCOTT, M.D.

We must begin with a consideration of the terms which it is necessary to understand before we can frame a definition of acidosis. Acids, alkalis, and salts are dissociable substances, the two companion ions of which they are formed parting company when they are in dilute solution. These companion ions are kations which carry a positive electric charge and anions carrying a negative charge. Acids owe their properties to the presence in their molecule of one or more hydrogen atoms, each of which can act as a kation when the acid is in watery solution, just as alkalis owe theirs to one or more hydroxyl ions (OH), each with a negative charge. A "strong" acid is one in which dissociation occurs readily, so that its solutions possess a high proportion of free hydrogen ions, while "strong" alkalis similarly have many free hydroxyl ions. "Weak" acids and alkalis are much less readily dissociable. Pure distilled water contains both free hydrogen and free hydroxyl ions, but in it the numbers of both types of ions are the same and the fluid is consequently neutral in character.

"NORMAL" SOLUTIONS.

"Normal" solutions are solutions which contain the combining weight of the substance in 1 litre of solution. In quantitative chemistry we compare different strengths of the same acid and acids of different "strengths" in terms of normality: thus 10 c.c.m. of normal acid, or 100 c.c.m. of decinormal, or the arithmetical equivalent of this, whatever be the acid, will exactly neutralise 10 c.c.m. of normal alkali. But in physical chemistry it is convenient to talk in terms of

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"strength" or "acidity"—i.e., in terms of free H-ions. The hydrogen-ion concentration, briefly spoken of as cH, is the weight in grammes of free H-ions per litre of solution—i.e., the normality of the solution in free H-ions. This weight is extremely small—e.g., in pure water it is approximately 0.000000097 g. per litre. It is inconvenient to write so many ciphers, and Sorensen therefore introduced the notation known as pH (potence or power of H). To explain this we may write down the normality of some solutions of hydrochloric acid, their cH and pH. A normal solution of hydrochloric acid contains 36.5 g. per litre, of which 1 g. is H and 35.5 g. Cl. In the case of this acid the hydrogen, even in strong solutions, is almost fully dissociated, and the dissociation of the water in which it is dissolved is comparatively negligible. (In any case these factors tend to cancel each other.) Consequently, we may say that in a normal solution of hydrochloric acid the H-ion concentration is 1. Similarly in a deci-normal solution the H-ion concentration is 0.1, and so on. The third column gives a simple arithmetical equivalent of the figures in the second column and the fourth column gives the "pH."

<table>
<thead>
<tr>
<th>Normality</th>
<th>cH</th>
<th>This may be written as</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 N</td>
<td>0-1</td>
<td>1/10³</td>
<td>1</td>
</tr>
<tr>
<td>0-01 N</td>
<td>0-01</td>
<td>1/10⁴</td>
<td>2</td>
</tr>
<tr>
<td>0-001 N</td>
<td>0-001</td>
<td>1/10⁵</td>
<td>3</td>
</tr>
<tr>
<td>0-0001 N</td>
<td>0-0001</td>
<td>1/10⁶</td>
<td>4</td>
</tr>
</tbody>
</table>

It will be readily recognised that the column headed pH gives the power to which 10 must be raised in order to get the number of litres of solution which contain 1 g. of free hydrogen ions. This, indeed, is a definition of pH; and it naturally follows that as the H-ion concentration diminishes the pH increases. If, however, you go on diluting an acid the H-ion concentration does not diminish indefinitely; because the diluting fluid, water, contains free H-ions; on diluting an acid to an infinite extent, the H-ion concentration approaches to that of pure water, which is 7.07 at ordinary room temperature. I have explained that pure water contains an equal number of hydrogen and hydroxyl ions. But a watery solution of acid contains a small number of hydroxyl ions derived from the water, and solutions of alkali contain some hydrogen ions. It is an interesting fact that in all water solutions—acids, neutral or alkaline—the number of hydrogen ions multiplied by the number of hydroxyl ions is always a constant—i.e., the number of hydrogen ions present is the inverse of the number of hydroxyl ions. Consequently, the number of hydrogen ions present can be used as a measure of the reaction of a solution even when this is on the alkaline side of neutrality. As a solution becomes more alkaline its pH increases from 7.07 to 14.14. The pH of arterial blood may be taken as 7.35 and that of venous as 7.33. Both are very slightly on the alkaline side of neutrality, and the difference between them is very small indeed. The reaction of the blood is maintained within these narrow limits in spite of the alternate addition and removal of about 6 per cent. by volume of carbon dioxide by means of the "buffers" of the blood. A buffer is the salt of a weak acid, solutions of which have the power of taking up limited amounts of comparatively strong acid with less change of reaction than would be the case if the buffer were absent. The simplest example is one of the buffers of the blood, though incidentally it is one which is of least importance in the carriage of carbon dioxide.

\[
Na_2HPO_4 + CO_2 + H_2O \rightarrow NaH_2PO_4 + NaHCO_3.
\]

It will be seen that the carbon dioxide is "mopped up" by the phosphate with formation of sodium bicarbonate. Naturally the reaction changes less than if it were not so "mopped up."

The plasma proteins act similarly. They are so-called "amphoteric electrolytes"—i.e., they may act as either acids or alkalis. In virtue of their acid properties they are combined in the plasma with base, and this base is liberated when carbon dioxide is added to the blood, the two combining together. The protein is such a weak acid that loss of its base does not materially affect the reaction of the plasma.

The haemoglobin of the red cell similarly acts as a buffer in the carriage of carbon dioxide, but in this case the base is potassium and not sodium. The wonderful economy of Nature is also illustrated here, for, just as nitrous is a weaker acid than nitric, so reduced haemoglobin is a weaker acid than oxy-haemoglobin. Consequently, when oxyhaemoglobin is reduced in the tissue capillaries some acid can be taken up in the blood without change in reaction by the base which is thereby liberated. Haemoglobin by its buffer action and by this change from a weak to a strong acid is responsible for the carriage of 84 per cent. of the carbon dioxide which is taken up in the tissue capillaries. Some of this carbon dioxide passes directly into the red cells and combines with the buffer base liberated there, but some of the buffer effect of haemoglobin is exerted indirectly as follows: Carbon dioxide reacts with sodium chloride in the plasma with formation of sodium bicarbonate and hydrochloric acid; the hydrochloric acid migrates into the red cell to combine with buffer base. This effect is known as the migration of chlorine ions and is sometimes called the Hamburger interchange.

The mechanism which we have been describing is the so-called primary buffering of the blood—i.e., that which is responsible for the buffering against carbon dioxide. The secondary buffering maintains the reaction of the blood when fixed acids, such as lactic acid, are added to the blood. The mechanism is as follows: The carbon dioxide which is added in the tissue capillaries and given off in the lungs forms only a small percentage of that carried in the blood. Even arterial blood contains some 50 per cent. by volume of carbon dioxide, this percentage being raised to 56 per cent. in the veins. A large volume of carbon dioxide is
Thus carried round and round the body. With the exception of a small amount of free carbon dioxide all this gas is combined with sodium as bicarbonate (NaHCO₃). When lactic acid is added to the blood it reacts with this bicarbonate, forming sodium lactate and free carbonic acid gas, which is now the relatively weak acid and, furthermore, is got rid of from the lungs.

The sodium bicarbonate which is carried round and round the body represents a reserve of alkali which is available for the neutralisation of any fixed acids which may be shed into the blood. This "alkali reserve" is measured by the volume of carbon dioxide measured dry and at N.T.P., which can be expelled from 100 c.c.m. of blood which has been brought into equilibrium with normal alveolar air (with a partial pressure of carbon dioxide equal to 40 mm. Hg), the volume of carbon dioxide in simple solution being deducted. It is to be noted that the pH of the blood is proportional to the ratio of free to fixed carbon dioxide—i.e., it is equal to a constant \( k \times \text{H}_2\text{CO}_3/\text{NaHCO}_3 \). This is known as the Hasselbalch formula.

**Definition of Acidosis.**

We have now considered all our terms and are in a position to define what we mean by acidosis. Two definitions have been given, which, though not coincident, are not necessarily exclusive. The official definition in this country is that acidosis (or "acidæmia") is a condition in which the reaction of the blood is shifted towards the acid side of the normal. Notice that this is not the same as "to the acid side of neutrality." Even in comparatively severe acidosis the blood is still alkaline. Van Slyke, on the other hand, defines acidosis as a diminution of the alkaline reserve; if this is accompanied by a corresponding diminution in the free carbon dioxide of the blood he calls the condition "compensated acidosis"; if not so accompanied the condition is " uncompensated " acidosis.

It seems simpler to use the word acidosis in its official sense, while referring to van Slyke's condition as simply one of "diminished alkali reserve." In the acidosis of carbon dioxide poisoning, as well as in the opposite condition of alkalosis caused by alkali ingestion, the alkali reserve is increased; while in the acidosis caused by ingestion of acids, as well as in the alkalosis of mountain sickness, the alkali reserve is diminished.

**Regulation of Reaction of the Body.**

This leads us naturally to consider how the reaction of the body as a whole is regulated. Normal metabolism results in a large daily production of carbonic acid gas, besides the phosphoric and sulphuric acids due to the oxidation of the phosphorus and sulphur in protein. The latter are not wholly neutralised by the alkaline salts of vegetable food, but must be excreted as salts. The channels of excretion are the lungs for carbon dioxide and the kidneys for salts, and the relative importance of these two channels is indicated by the fact that while about 40 litres of normal acid in the form of carbonic acid gas are excreted per day by the lungs, the kidneys excrete the equivalent of about 150 c.c.m. of normal acid. The lungs act as the coarse adjustment for the reaction of the body, and the kidneys as the fine. The kidneys excrete the acid in the form of acid salts, chiefly acid sodium phosphate (NaH₂PO₄), the reaction of the urine being adjusted by the relative proportions of di-sodium hydrogen phosphate and sodium di-hydrogen phosphate. A third important factor in the maintenance of the reaction of the body is the ammonia produced by the liver. Normally about 0-7 g. of ammonia are excreted in the urine per diem. This serves to aid in neutralising the fixed acids produced in the body, but if for any reason an excess of acids is being produced, or if there is a diminution of the base of the body, the body saves up alkali for itself by increasing the formation and excretion of ammonia. Ammonia thus acts as an alternative base, sparing the fixed base. The body cannot protect itself by accumulating ammonia while maintaining the ordinary excretion of fixed base, for ammonia is toxic.

This leads us to speak of one of the simplest tests for acidosis. With phenolphthalein as an indicator a known volume, say 20 c.c.m., of urine is titrated to neutrality with Na/10 alkali. Neutralsed formalin is then added. This reacts with the ammonium salts with the liberation of an equivalent amount of acid and formation of urotropin. Owing to the liberation of acid the red colour of the phenolphthalein disappears; the titration with alkali is continued until it returns. The total Na/10 alkali used should not exceed the volume of urine taken and used for the estimation. If it does, acidosis is present and its severity is proportional to the excess of alkali used.

Acidosis, or a tendency thereto, commonly occurs when the oxidations of the body are interfered with, with the consequent production of fixed acids instead of gaseous carbon dioxide. If the oxidation of carbohydrate be interfered with, its intermediate breakdown product, lactic acid, escapes into the blood-stream; there is a diminution in the alkaline reserve and a tendency to alkalosis in the official sense. Commonly, however, acidosis is associated with another condition, ketosis. This occurs when the oxidation of fats is interfered with. Fatty acids consist of long chains of carbon atoms, each of which usually carries two hydrogen atoms. The terminal group is carboxyl.

\[
\begin{align*}
\text{H} & \text{H} \text{H} \\
\text{H} & \text{C} \text{-} \text{C} \text{-} \text{C} \\
\text{H} & \text{H} \text{H} \\
\text{H} & \text{C} \text{-} \text{C} \text{-} \text{C} \\
\text{H} & \text{H} \text{H} \\
\text{C} & \text{-} \text{C} \text{-} \text{C} \\
\text{C} & \text{H} \text{H} \\
\text{H} & \text{H} \text{H} \\
\end{align*}
\]

This represents a saturated fatty acid. (The fatty acids which occur in the body contain an even number of carbon atoms.) The carbon atom next the carboxyl group is called the alpha carbon atom, the next one the beta carbon atom, and so on.
An unsaturated fatty acid is one in which two adjoining carbon atoms have each lost one hydrogen atom and are united by a double bond—

\[ \text{CH}_3-\text{CH}==\text{CH}-\text{CH}_3 \]

This is a weak spot in the chain. Usually the double bond is between the alpha and the beta carbon atoms and breakdown occurs here, resulting in the oxidation of the two terminal carbon atoms and the production of a fatty acid having two less carbon atoms. This shorter acid is again broken down by beta-oxidation, and so on, until the four-carbon stage of the fatty acid is reached. Here an extraordinary, though not inexplicable, phenomenon occurs; the oxidation of the four-carbon fatty acid requires the simultaneous or "linked" oxidation of a molecule of glucose (under the most favourable conditions the molecular proportion may be 2 fatty acid : 1 glucose). If the oxidation of glucose be interfered with, so also is the completion of fat katabolism. A result of this interference is the appearance of acetone or ketone bodies, representing incomplete oxidation of butyric acid.

\[ \begin{array}{c|c|c|c}
\text{CH}_3 & \text{CH}_3 & \text{CO}_2 & \text{CH}_3 \\
\text{CH}_3 & \text{CHOH} & \text{CO} & \text{CH}_3 \\
\text{CH}_3 & \text{CH}_2 & \text{CH}_3 & \text{CH}_3 & \text{COOH} & \text{COOH} & \text{COOH} & \text{COOH} \\
\text{Butyric} & \text{Beta-hydroxy-} & \text{Aceto-acetic} & \text{Acetone.} \\
\text{acid.} & \text{butyric acid.} & \text{or diacetic acid.} \\
\end{array} \]

These are injurious in two ways: (1) they react with bicarbonate, diminishing the alkali reserve and causing a tendency to acidosis; (2) more important, they contain the toxic enol group. The appearance of these substances in diabetes is an indication that the amount of glucose being oxidised is insufficient to complete the oxidation of the fats of the diet, either because the interference with the oxidation of glucose is so extreme, or because the glucose intake has been cut down to too low a level, so that, after the leakage of a certain proportion owing to the hyperglycaemia, an insufficient amount remains to complete the oxidation of fats. Roughly this means that the weight of fat fed must never exceed four times the weight of glucose oxidised (safer not to exceed twice); but the subject of the ketogenic-anti-ketogenic ratio is a thorny one, and I refer those interested to a summary of the subject by Shaffer in the issue of Medicine for November, 1923.

Every practitioner should have in his consulting-room the reagents necessary for testing for acetone and diacetic acid. A fresh solution of sodium nitroprusside is prepared by dissolving a crystal in water; 10 c.c.m. of the suspected urine is saturated with ammonium sulphate by adding 5 g. of the crystals; 3 drops of the nitroprusside solution and 2 c.c.m. of strong ammonia are added. A fine permanganate colour is produced if acetone or diacetic acid is present.

**Acidosis in Children.**

I leave it to yourselves to apply the theoretical considerations which I have indicated. I will content myself with emphasising the frequency of slight cases of acidosis in children. It is obvious that any interference with normal oxidations results, as I have said, in a tendency to acidosis. This occurs in many quite trivial, as well as serious, complaints in children. The metabolic derangement caused by extreme fatigue or excitement, such as a railway journey, may bring it on. These conditions may be responsible for the upset which occurs on the first day or two of a holiday, an upset which is often attributed to change of air. Sometimes it is so serious that the parent takes the child home again to consult his own doctor, only to find that the return home is not accompanied by improvement but rather a temporary worsening.

The treatment is obvious. Rest in bed will diminish the metabolic exchange and give time for the condition to improve, as it does, spontaneously. The diet must be carefully attended to; fatty foods must be avoided; while bread-and-milk or dry toast or almost any of the patent invalid foods supply an adequacy of carbohydrate for forcing the completion of the oxidation of fat.

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**The Silhouette Radiogram in the Interpretation of Clinical Signs.**

**By A. P. BERTWISTLE, M.B., Ch.B. LEEDS, F.R.C.S. EDIN., Director of the Post-Graduate Hostel.**

When a sharply cut outline is required a photograph or drawing comes far behind a silhouette in many respects. It is not as well known as it should be, that it is a very simple matter to prepare a silhouette from a radiogram. The superimposition of the contour of the part on that of the bone possesses great teaching possibilities which are worth studying.

It is a recognised fact that in the process of ordinary printing the fleshy contour of a part, which was quite definite on the negative, disappears. The silhouette radiogram is prepared as follows: The plate or film is held to the light, or better, placed in a viewing-box, and the outline of the part is scratched on it by means of a mounted needle. When a print is made this outline appears as a

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*Opening remarks at a Discussion at the Post-Graduate Hostel, July 19th, 1926.*