"ACIDOSIS" AND HYDROGEN-ION CONCENTRATION.

BY

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IN Professor Moore's second paper¹ he carries on the problem of "buffer salts" to the important practical connexion it has with the state called "acidosis" and with the appropriate treatment thereof. The question is discussed in some detail in a forthcoming memorandum of the "Shock" Committee, which will soon be placed by the Medical Research Committee at the disposal of those interested. But it may serve a good purpose if I attempt, as briefly and simply as I can, to place the main points of the discussion before the judgement of the readers of this JOURNAL. Before doing so I may be permitted to reply to Professor Moore's criticism of my previous statements so far as they refer to the relative importance of the proteins and the bicarbonate in the blood.

When Fernbach and Hubert used the word "tampon," we may surely assume that they were aware of its meaning. Littre's *Dictionnaire de Médecine*, after stating that "tampon" is used for "tamponnement," describes the latter thus:

Introduction de bourdonnets ou de tampons de charpie, secs ou imbibés de liquides hémostatiques, dans une plaie ou dans une cavité naturelle, telles que l'utérus, le vagin, les cavités nasales, pour arrêter une hémorrhagie.

As I remarked before, the word is not altogether satisfactory for the purpose of the authors named, but it is better than "buffer." However, I adhere to my opinion that neither is required in the case of the blood.

Claims of priority in such matters are rather sterile and lead to little profit. It must be admitted that the work of Professor Moore and his colleagues has not received the attention it deserves, but may I point out to him that the titles of the papers scarcely suggest that the method by which the neutrality of the blood is preserved is discussed therein?

The experiment suggested at the top of p. 253 has actually been done. With what result? In the *Journal of Biological Chemistry*, vol. vi (1909), Brailsford Robertson put forward the same view as Professor Moore has done, but without referring to his work. Lawrence Henderson replied in the succeeding volume with calculations showing that the effect of protein must be very small compared to that of the bicarbonates. Robertson then performed the actual experiments, and honourably admitted that he was wrong. He states (p. 356) that between the reaction of normal blood and that of "advanced acid intoxication" "the proteins of the blood are about one-fifth as efficient as the bicarbonates in maintaining its neutrality." These experiments were done by the use of the hydrogen electrode, and their accuracy cannot be denied. Professor Moore, on the contrary, holds that 90 per cent. of the effect is due to the proteins.

There is no doubt that proteins can combine with acids and bases in strength beyond this range; but, as Professor Moore admits, the turning point of methyl-orange is at a reaction incompatible with life. The chemical change to which I referred is merely that of an internal anhydride to an open form, easily reversible by the removal or addition of the elements of water.

The experiment of adding a drop of acid to serum and noting that the change of colour produced returns to its original tint on exposure to air is of interest because it shows that the increase of acidity is due to carbon dioxide set free. If it does not come from bicarbonate, what is its source? No evidence has been given against that quoted as a proof that proteins do not combine with carbon dioxide.

The giving off of carbon dioxide to a vacuum does not really touch the present question, because the blood is not exposed to zero tension of carbon dioxide in the lungs and at the actual alveolar tension no bicarbonate is dissociated. I quite agree that "acidosis" cannot be determined by driving off the carbon dioxide by sulphuric acid in a vacuum, for the reason to be seen presently.

I must ask pardon of Professor Moore for misunderstanding him as to the kind of union he believes to exist

between the salts and colloids of blood serum. It appears that he does not mean chemical combination but physical juxtaposition, in fact, what most people now call "adsorption." Much confusion is caused by the use of the word "combination" for this. But I do not admit that it is an error to say that the sodium and chlorine ions in a solution of sodium chloride are not in "chemical union." If they are, what is the difference between the dissociated and undissociated molecules? The reason why the ions cannot be separated without the expenditure of a great amount of energy was pointed out by Arrhenius to be the physical electrostatic attraction between oppositely charged bodies. The use of the expression "chemical combination" should be restricted to those cases where there is a change in the nature of the atoms concerned, such a change as implies alteration in their internal structure and energy.

However, I cannot agree that the salts are in a state of adsorption on the surface of the proteins. Adsorbed substances take no part either in osmotic pressure or in electrical conductivity. The reason why gum solutions are so much more effective in maintaining blood pressure is not because they hold back the salts from escape, but because they hold back the water. As Scott showed, the wall of the blood vessels is normally permeable to salts and water, not to colloids; hence the osmotic pressure of the latter is effective in holding back the water from leakage to the tissues.

The paragraph with reference to the production of toxins and so forth has nothing to do with the maintenance of neutrality and confuses the issue. The advocates of "acidosis" as an important factor in pathological conditions assert that it is the state itself that is responsible. But what do they mean by it?

The introduction of the names "acidosis" and "acidæmia" can only be regarded as a misfortune to the interests of clear thinking. If they mean anything, they imply that the blood becomes acid. It does not improve matters when Van Slyke defines acidosis as a state in which the sodium bicarbonate of the blood has become reduced below a certain value. The question is, Does the introduction of acid into the blood, whether by formation in the tissues or by intravenous injection, increase the "acidity" of the blood to any perceptible degree, or is it of itself a matter of any real importance? I regret to notice that Professor Moore himself uses the word "acidity" when he merely means a change in the available alkali of the blood, because Sir Almroth Wright's method of titration determines this and no more.

This property which we call "acidity," common to all acid substances, is the presence in their solutions of hydrogen ions arising from their greater or less electrolytic dissociation. Different acids vary in this, and it is no small advantage of the use of the expression "hydrogen-ion concentration" that it gives us in absolute numerical expression the strength of an acid.

Now, when acid comes into the blood, does it change for more than a brief period of time the hydrogen-ion concentration? This is the crucial test, since all the physiological and pathological effects described as due to acid are effects of hydrogen ions in increased concentration. That none of these effects are produced by the introduction of acid into the blood is shown by the experiments of Dale and Richards, which will be found described in detail in the memorandum to be published. I may merely say here that large quantities of acid were injected into cats intravenously, enough to produce what Van Slyke's method would indicate as a very severe acidosis, since the bicarbonate was reduced to a very low level. On recovery from the anaesthetic, these cats ran about and showed no abnormal signs. Some experiments which I made myself throw light on the reason why this was so. A sample of blood was taken from a cat under urethane, the plasma centrifuged off under liquid paraffin, and a drop of neutral red added. The colour was the orange tint of neutrality. Acid was then introduced into a vein in amount sufficient to neutralize one-third of the bicarbonate. Temporary hyperpnoea resulted, as in Dale and Richards's cats. Another sample of blood was taken a little later and the reaction to neutral red was found *unaltered*. Neutral red is very sensitive to a slight change in hydrogen-ion concentration at the region of the reaction of blood and would easily have indicated it, if present. There was no increase in the hydrogen-ion concentration, although the

bicarbonate was reduced. In other words, there was "acidosis" without any change in the "acidity."

Dale and Richards produced acidosis without any harm, because there was no increase in the hydrogen-ion concentration. The explanation should be obvious. Lawrence Henderson pointed out that the hydrogen-ion concentration of a bicarbonate solution containing dissolved carbonic acid depends on the relative proportion of the bicarbonate itself to the carbonic acid. The bicarbonate is the alkali which balances, as it were, the presence of the acid. If we diminish the bicarbonate, therefore, we can keep the hydrogen ion constant by removing carbon dioxide. When acid obtains entrance into the blood it drives off carbon dioxide from a part of the bicarbonate, forming the sodium salts of the acid. There is a temporary increase in the hydrogen ion from the excess of carbonic dioxide, but this increase is far less than the acid itself would have produced in the absence of bicarbonate, because carbonic acid is an extremely weak acid and very little dissociated. All the same, the respiratory centre is so sensitive to the slightest increase of hydrogen-ion concentration that the increase in carbon dioxide referred to is sufficient to stimulate it. This excess of carbon dioxide is rapidly removed by the respiratory ventilation of the lungs, and as soon as enough has been removed to make up for the decreased bicarbonate the respiratory centre ceases to be stimulated, because the hydrogen ion has become normal. Such experiments show the actual state of affairs in the living organism, whereas methods of determining merely the bicarbonate reserve in the blood after exposure to the air or to a particular tension of carbon dioxide, give no information as to the hydrogen-ion content in the organism, because they take no account of the respiratory compensation. When we remember that acids are produced by deficient supply of oxygen to the tissues, we see how appropriate the increased ventilation is.

It may be said that if the sensibility of the respiratory centre is depressed, such a compensation may be inadequate. To test this, I repeated the previous experiment under a large dose of morphine, so that the respiration was reduced to five or less a minute. The result was a marked fall in the bicarbonate reserve, but the change in hydrogen-ion concentration, although detectable, was very minute. It was far less than necessary to produce any of the pathological results ascribed to acidosis.

Corresponding experiments may be done with serum *in vitro*. Adding acid in quantity sufficient to neutralize one-half of the bicarbonate causes an increase in hydrogen ion if compared with normal serum after bringing both into equilibrium with my own alveolar air. But if the tension of the carbonic acid in the air with which the more acid serum is brought into equilibrium is reduced to one-half that of alveolar air, then the hydrogen ion is brought to the same point as the normal serum in equilibrium with normal alveolar air. This is within the limits of respiratory capacity. Henderson and Haggard have shown that to maintain the hydrogen ion constant when the bicarbonate falls by one-third, 50 per cent. more ventilation only is required.

The capacity of regulation towards alkali is more limited in the living animal. I performed an experiment similar to the acid one, but injecting bicarbonate instead of acid. Neutral red is yellow in bicarbonate solution, which is therefore alkaline to it. A sample of blood taken forty minutes after the end of the injection, which had been given slowly, still gave a yellow colour with the indicator, showing an abnormal degree of alkalinity. This is perhaps to be accounted for by the fact that to compensate the increase in bicarbonate, less carbon dioxide than normal must be given off by the lungs; this would also mean a decreased supply of oxygen to the blood, a mischievous effect. It shows that the injection of alkaline solutions is to be deprecated, unless care is taken that the normal bicarbonate content of the blood is never exceeded. Too low a hydrogen-ion concentration is as bad as, or worse than, too high a concentration, because it is less easily rectified by respiration, and physiological processes are just as sensitive to one as to the other.

Professor Moore states that Cannon found a decrease of bicarbonate reserve in wounded men in France. This I admit, since I was present at some of the determinations, but it does not prove that this was the cause of the low blood pressure in these cases of shock. Indeed, Cannon

was always alive to the possibility that the low blood pressure was the cause of the production of acid, and further investigation has convinced him that this is the correct explanation. It is remarkable that Wright and Colebrook (*Lancet*, June 1st, 1918), although they recognized deficient blood supply as a cause of "acidaemia," instead of recommending methods of improving the circulation by the injection of appropriate liquids which do not leave the blood vessels, should have recommended merely solutions of sodium bicarbonate. This certainly neutralizes acid after its formation, but has no effect in diminishing its further production, except by the raised blood pressure during the short time that it, like any other saline solution, remains in the blood vessels. A positive objection to it is that, by diminishing the hydrogen-ion concentration of the blood, it depresses the respiratory activity and leads to a lower oxygen supply at a time when more is needed. In no form of experimental shock have I found injection of bicarbonate of benefit, whereas a solution of gum in 0.9 per cent. saline, even when slightly acid, is nearly always curative.

Decrease of bicarbonate in the blood is not, then, of importance in itself, and the only practical value of determination of its degree, whether by Van Slyke's or by Wright's method, is to indicate deficient oxidation in the tissues. It shows the necessity to improve the blood flow, and recent experience seems to indicate that what is needed is only a solution which will permanently increase the volume of the blood; there is a reserve of haemoglobin, unless the loss of blood has been exceptionally great. The important practical problem of when transfusion of blood is required, and when gum alone suffices, is still under discussion.

REFERENCE.

¹ BRITISH MEDICAL JOURNAL, September 7th, 1918, p. 251.

Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

CELLULOID SOLUTION FOR TRACTION.

(Abstract.*)

For the past three months experiments have been made with a 5 per cent. solution of celluloid in acetone, which we have found makes an excellent adhesive material; 7 or 8 per cent. may be used where only small areas of skin are available.

The required amount of celluloid scrap and acetone are placed in a dry, clean, wide-mouth bottle, securely stoppered, and shaken at intervals. The solution is ready for use in forty-eight to seventy-two hours, and when properly made is an almost clear homogeneous, syrupy fluid.

The skin should be absolutely dry. A layer of celluloid solution is rapidly applied by a small brush. The quantity should be sufficient to soak through the strip on which traction is to be applied, and a thin coating is applied externally to get out all the wrinkles and air bubbles. Canton flannel is the best material for strips, but a double layer of gauze or muslin that is neither too hard nor too finely woven, may be used. The application of iodine, picric acid and alcohol to areas to which any type of adhesive is to be applied should be avoided as far as possible. If there is delay in putting on the strip, the skin should be recoated, for it dries out in a thin flexible film in a minute or two. The application of a circular gauze bandage increases the effectiveness of adhesion. The solution is combustible, and it is therefore advisable to label bottles properly.

Twenty-five applications of this solution have been carefully observed and it is believed that the scope of traction is increased by its use.

CONCLUSIONS.

The conclusions founded on the cases reported in the full paper are as follows:

1. Six per cent. celluloid in acetone makes an excellent adhesive material.
2. Its rapidly volatilizing quality permits of immediate traction.

*The full paper has been forwarded for publication in *Surgery, Gynecology, and Obstetrics*.