incline rising 30 feet vertically; but the clerk, whose hourly muscular work is measured in hundreds rather than in thousands of foot-pounds, might very well manifest symptoms of distress if forced to take the same run.

We therefore propose to use the word "strain" as a convenient term for the risk to which a man is exposed who does muscular work considerably in excess of that to which he is habituated, and to use the word "strenuous" for habitual heavy labour. In this sense, all the heavy occupations in our list involve strenuous work and in most cases there is also the liability to strain. The railway goods porter, for example, is habitually accustomed to strenuous work, but at any time the moving of an unexpectedly heavy load or the slipping of some weighty piece of goods which he is handling may expose him to strain. While we have endeavoured to ensure that all men whose occupations are strenuous in the sense defined above are classified in the heavy labour groups, it is obvious that many of the cases exposed to strain are necessarily placed in the medium, light, and sedentary occupations groups. Since, in every case, the habits of the recruit with regard to exercise were inquired into, the records have enabled us to form some sort of an estimate regarding the exposure to strain, and a careful inspection of the individual records induces us to believe that out of the 10,000 recruits examined, 2,711, that is to say 27.1 per cent., were subject to strain as defined above, either in their work or in their amusements.

With a view to representing our results in as concrete a form as possible, we append tables of the percentages and correlation figures we have found for our 10,000 cases.

Percentages.

History of rheumatic fever...	19.2	History of diphtheria ...	7.2
" chorea ...	2.6	" pneumonia ...	5.3
" "rheumatism" ...	16.1	" influenza ...	56.0
" growing pains ...	26.5	" syphilis ...	2.0
" tonsillitis...	22.1	" gonorrhoea ...	5.95
" scarlet fever ...	21.8	" strain ...	27.1

Correlation Figures.

Correlation between History of	Coefficient.	χ^2 .	Degree of Correlation.
Rheumatic fever and chorea ...	0.31 ± 0.02	63.0	Moderate.
Rheumatic fever and "rheumatism" ...	0.08 ± 0.02	9.2	Negligible.
Rheumatic fever and growing pains ...	0.06 ± 0.02	9.7	"
Rheumatic fever and tonsillitis ...	0.13 ± 0.02	38.0	Low.
Rheumatic fever and scarlet fever ...	0.08 ± 0.02		Negligible.
Scarlet fever and diphtheria ...	0.27 ± 0.002	101.0	Moderate to low.

THE REACTIVITY OF THE BLOOD

IN RELATION TO CARDIAC BREATHLESSNESS, SURGICAL SHOCK, AND ALLIED CONDITIONS OF THE NERVOUS AND CIRCULATORY SYSTEMS.

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The plasma of the blood possesses the remarkable property of being able to neutralize large amounts of either acid or alkali without itself being or becoming markedly acid or alkaline. This property ensures the immediate neutralization of acidic or alkaline metabolites thrown into the blood stream as the result of physiological or pathological processes. Without this protection the life of the human race and all the higher animals and plants as at present constituted would be impossible, for it has been shown by the researches of Moore, Roaf, and Whitley¹ that the strip of variation in acidity or alkalinity within which life is possible is a very narrow one, and that it suffices to render the medium within which living cells are situate acid or alkaline to the feeble limit of one-thousandth normal, or less, in order to destroy all life.

It will suffice to give a few illustrations of the importance of small variations in this property of balanced alkalinity and acidity (or hydrogen ion concentration, as it is termed in the language of physical chemistry) in order to prove the necessity of a clear understanding of the problem by physiologists and clinicians alike, and, since the recent communication of Professor Bayliss² clearly demonstrates that there is not agreement either as to facts or interpretations regarding the cause or mode of operation of this protective influence, some service may be rendered by a discussion of the question and a reply to his criticisms.

When Haldane and Priestley³ discovered that the respiratory centre was most delicately balanced in relationship to the concentration of carbon dioxide in the blood, it was sought to correlate the increased respiratory activity after muscular exercise with the production of lactic acid and other organic acids by the muscles, and much research was expended on the determination of lactic acid in blood and urine. At an early discussion of the subject at a meeting of the Physiological Society the present writer suggested that the increased acidity or hydrogen ion concentration of the plasma due to increased dissolved carbonic acid was quite sufficient to form an adequate stimulus to the respiratory centre without any invocation of lactic acid or other organic acid. After some years of vain searching for increase in lactic acid or other partially oxidized metabolites, it has now been proved by the labours of Barcroft, Peters,⁴ and others that this is the correct explanation of the regulation of respiratory activity.

An interesting corollary to this physiological discovery is the recent clinical one by Lewis, Cotton, Barcroft, Milroy, Dufton, and Parsons⁵ that breathlessness in soldiers suffering from irritable heart is accompanied by a condition of acidosis of the blood. It has been shown by these observers that the blood plasma of such patients possesses less protective power against carbonic acid, or other acid, than that of normal individuals, for the addition of acid causes a quite disproportionate rise in hydrogen ion concentration—that is to say, in that acidic property which stimulates the respiratory centre. Accordingly such patients become breathless on much less exertion than ordinary individuals because they are deficient in alkaline reserve with which to combine the carbonic acid set free by the muscles. As will be pointed out later, this acidic condition of the blood is communicated to all the nerve and muscle cells, voluntary and involuntary, bathed by the altered plasma, and a pathological condition is induced in these, so that their irritability is increased like that of the nerve cells of the respiratory centre. At a deeper stage the increased excitability passes into shock accompanied by physico-chemical changes in the proteins of plasma and cell protoplasm, which will presently be described.

Another interesting development of the problem is that different varieties of shock to the system, such as haemorrhage, surgical operation, infection of wounds, and gassing by irritant gases, are accompanied by acidosis or deficiency of alkali reserve, and when once this vicious condition has been established it gives rise to physico-chemical alterations in plasma and cell protoplasm which tend to retain the circulatory system in a relaxed condition, and this relaxed condition in turn keeps up the acidosis through the stagnation of the circulation. The presence of acidosis in conditions of shock, and its influence in lowering arterial blood pressure was shown by Yandell Henderson⁶ and others in America prior to the war, and quite recently has been amply confirmed by Cannon in observations on wounded in casualty clearing stations in France.

A similar drop in the alkali reserve of the plasma following prolonged anaesthesia and operation has been established by many American surgeons, such as Crile and Menten,⁷ Austin and Jonas,⁸ Morris,⁹ and Caldwell and Cleveland.¹⁰ The danger of surgical shock followed by coma and death in diabetes, where there exists high acidosis accompanied by defect of alkali reserve, is known to all surgeons. It has recently been proven by Sir Almroth Wright¹¹ that there is a marked increase in acidity of the serum in gas gangrene, termed by him "acidemia," and that the bacillus of this disease flourishes with ease in partially neutralized serum, but is inhibited by serum of normal alkalinity. A similar condition in severe cases of gassing in soldiers and of experimental

gassing in animals has been observed by Barcroft and his co-workers.

In the history of the subject this protective action has received many names, such as "tampon effect," "reactivity of the plasma," "buffer salt effect," "alkali reserve," "acidosis," "acidaemia," "balanced neutrality," "balanced hydrogen ion mixture," "hydrogen ion regulation," and all these are merely attempts at naming and defining the same property.

There is no evidence, either by direct statement or inference, that the French writers, Fernbach and Hubert,¹² who first used the word "tampon," had in mind, as suggested by Professor Bayliss, "a plug of cotton-wool pressed into a wound or elsewhere in order to stop bleeding," and Professor Sørensen of Copenhagen probably transmitted their meaning quite correctly when he used it in the meaning of a buffer, and translated it into German as "puffer."

This paper by the French authors is a short one of a little over two pages in the *Comptes rendus de l'Académie des Sciences*. It deals almost entirely with the protection of proteolytic enzymes by alkaline phosphates from destruction by acidity developed by their own action. The only reference to blood serum is in a single sentence, in which it is mentioned with other physiological fluids, as probably being protected by alkaline phosphates; there is not a single titration or mention of hydrogen ion concentration throughout the entire paper, no protective action of sodium bicarbonate or proteins is even hinted at, and there is certainly no exposition of the manner in which balanced neutrality is maintained.

As this is the only paper which can claim priority of description of the protective action of the blood plasma over those issued from the Liverpool School of Biochemistry in 1905 and 1906, lest it should be thought that a biased opinion is here being given of its importance, a statement may be quoted from a paper recently issued in the official publication of the Copenhagen school from Professor Sørensen's own laboratory. This paper, by J. Hempel,¹³ is written in English, and states: "The term 'buffer' ('tampon') was first introduced by Fernbach and Hubert to meet a special case; as already mentioned, however, it is in the works of S. P. L. Sørensen and Henderson that the great importance of such buffer mixtures for the organism was first thoroughly dealt with."

Now the first paper by Sørensen on this subject which a careful study of the literature has revealed appears in vol. viii of the above-cited publication in 1909, and his extensive monograph in German in *Ergebnisse der Physiologie* (Bd. xii, 1912). The two earliest papers by Henderson¹⁴ and his co-workers (1906 and 1907) deal almost entirely with equilibria in mixtures of alkaline and acid phosphates, which are practically non-existent, as admitted by Bayliss, in blood plasma. On the other hand, the first papers from the Liverpool School by Moore, Roaf, Whitley, Alexander, and Kelly¹⁵ contained (1905) a full account of the balanced neutrality of hydrogen and hydroxyl ions, both in blood plasma and in the case of living organisms developing in sea water, gave a lengthy description in the language of physical chemistry and ionic dissociation of how the equilibrium of hydrogen ions was maintained, and how this protected the marine organism or higher animal from poisoning by acid or alkali. The effects of alteration in the balance of acid and alkali in causing pathological variations in growth and cell division were also given in this first paper.

In a second paper by Moore and Wilson¹⁶ (1906), in vol. i of the *Bio-chemical Journal*, then first appearing from the Liverpool Laboratory, a clinical method was given for estimating the value quantitatively of the protective action by titrating from one given point of hydrogen ion concentration to another, these being marked by the turning points of colour of two selected colour indicators. In a long series of papers published in the earlier volumes of the same journal these researches were extended, and the effects of acid and alkali and neutral salts upon the physico-chemical properties of the serum proteins and other colloids were studied.

In giving this brief summary of the history of the subject the writer has no intention of belittling the magnificent work of the Carlsberg school under the leadership of Sørensen, which has in the colorimetric method of measuring the hydrogen ion concentration of physiological solutions provided such a rapid and powerful engine of research, nor that of the Harvard school under L. J.

Henderson, which has supplied so many exact studies of this important property. I give the credit due for pioneers' share in the work to many colleagues in earlier days at the Liverpool school; the main findings for which priority is claimed may be briefly enumerated, especially since some of them even now are unknown in the current literature of the subject.

1. It was shown that the physiological life of organisms and their normal development was only possible when the reaction of the nutrient fluid lay close to the neutral point, more than traces of alkali or acid beyond the neutralization points of the amphoteric salts and proteins sufficing to destroy life.

2. A disturbance of the balance towards the alkaline point, short of lethal doses, excited living cells to enhanced activity, and caused irregular growth and pathological cell divisions.

3. A clinical method was introduced for titrating the whole serum, including proteins, between two fixed points of hydrogen ion concentration, and also for titrating the alkaline inorganic salts alone of the serum after destruction of the proteins by incineration. Between these two points the hydrogen ion concentration, or intensity of acidity, varied very slowly, never surpassing about one in two-hundred-thousandths normal of excess of hydrogen or hydroxyl ion concentration, but outside the limits hydrogen or hydroxyl ion concentration arose very rapidly. The whole serum showed an amphoteric range of 0.15 normal, while the salts alone, without the proteins, showed a range of only 0.03 normal, thus indicating that the proteins are about five-fold as powerful as the bicarbonates and phosphates present in regulating reaction or hydrogen ion concentration.

4. The molecular concentration of 0.15 normal, which indicates the power of the proteins for combining with acid or alkali is equal to the molecular concentration of the serum for all the inorganic salts of the serum. This indicates that the delicate salt regulation of the plasma, a physiological process seen from the teleostean fishes up to mammalia, is based upon that amount of salts which satisfies the labile combining power of the proteins, and that any salt completely free, and not held in labile union in the plasma is excreted by the kidneys.

5. The neutralizing power of the serum proteins was tested under pathological conditions, and it was found that there was a definite increase in the alkaline limit in carcinoma, and this was correlated with the reduction in acidity of the gastric secretion.

6. It was found that just at the neutral point the osmotic pressure of the serum proteins fell absolutely to zero, indicating a change in the state of aggregation of the protein approaching to precipitation.

At the time these observations were being published all methods of titration were being flouted by German observers, who were working at electrical methods of measuring hydrogen ion concentrations, and Rudolf Höber¹⁷ goes so far as to describe titrations for acidity or alkalinity as ridiculous nonsense. The writer maintained that hydrogen ion determinations alone gave no complete indication, and that the all-important point was the resistance to disturbance by added alkali or acid of the hydrogen ion concentration of the physiological fluid. This could only be settled by titration values, and accordingly Moore and Wilson titrated between two points—namely, neutrality to phenol-phthalein and neutrality to di-methyl-amino-azo-benzol, and termed the result the "reactivity of the serum." This figure measures the resistance of the serum to acid or alkaline invasion and, throughout the range it measures, the change of hydrogen ion concentration is slow to added acid or alkali, while outside the range the change is very rapid, with accompanying pathological changes in any living cell bathed by the fluid.

Now that these preliminary considerations have cleared the ground, the criticisms made by Professor Bayliss may be considered. A fundamental point of difference arises when he states that "in its behaviour towards acids the plasma reacts precisely like solutions of sodium bicarbonate." The following considerations and a very simple experiment based upon them prove conclusively that this is not the case. The classical analyses of human and other mammalian serums by Carl Schmidt and by Bunge,¹⁸ when calculated out as basic and acidic equivalent weights, yield an excess of base amounting to a 0.04 normal solution in the plasma. Again, the determinations of Moore and Wilson give an alkalinity for the salts of the serum of 0.03 normal, and the recent determinations of Van Slyke and Cullen give very close agreement with this, showing an alkalinity of 0.025 to 0.030 normal. Now let all this be taken as present as sodium bicarbonate in the plasma, and to make a large margin for possible error let the amount be increased to 0.05 normal. Take now a quantity of Ringer's solution containing the equivalent of the neutral salts of the plasma, and add to it a sufficient amount of dry sodium bicarbonate to make it a 0.05 normal

solution of sodium bicarbonate—that is, add 0.42 gram per 100 c.cm. If the view held by Professor Bayliss is correct this solution ought to behave precisely like blood serum, while my contention is that it will behave quite differently to either acids or bases, weak or strong. Let the two solutions—serum and sodium bicarbonate in Ringer's solution—be each titrated (a) to standard acid, and (b) to standard alkali, with appropriate coloured indicators, or, if it be preferred, let the variations in hydrogen ion concentrations be measured by the hydrogen electrode method after equal successive additions of standard acid and alkali, and it will be found that the sodium bicarbonate solution is at least threefold as sensitive to added acid or alkali as is the serum, so that it would be a correspondingly poor protection to the tissue cells against any invasion by acid or alkali. Both the sodium bicarbonate solution and the serum will be found to give the acid reaction to phenol-phthalein, and the alkaline reaction to methyl orange or methyl red; but if, say, 10 c.cm. of each fluid be taken and titrated first with decinormal acid in presence of methyl orange it will be found that the colour changes sharply in the case of the bicarbonate solution when 5 c.cm. of the standard acid has been added, whereas the change in colour in the serum does not appear until at least 15 c.cm. of standard acid has been added, and then comes exceedingly slowly, so that the mid-point is not reached until about 18 c.cm. has been added. If now the alkaline limits be estimated by titration with decinormal alkali in presence of phenol-phthalein, a similar result will be obtained; a single drop, or at most two drops, of decinormal alkali will give a bright pink in the sodium bicarbonate solution, showing that alkalinity to this indicator has been attained, but no pink will be given by the serum until between 2 and 3 c.cm. of the standard alkali have been added. Surely these results indicate a considerable difference in behaviour between serum and a solution of sodium bicarbonate. Moreover, the results are not due, as Professor Bayliss supposes, to an attack upon the structure of the protein molecule by the strong acid, because the titration backward and forward with acid and alkali can be made as often as desired without any change in the properties of the serum proteins; secondly, the drops of acid or alkali immediately they enter the fluid under titration change their hydrogen and hydroxyl ion concentrations to the level of these in the fluid; that is, indeed, the whole point of the protective action, "tampon effect," or whatever it may be called, otherwise there would be no protection for the cells. If such a change did not occur, the colour indicator would at once react and alter colour, as indeed it does where the drop of standard acid or alkali enters, but the colour disappears again as mixing occurs. There is no point in the titrations as above where the acidity or alkalinity as indicated by hydrogen ion concentration rises above that of a solution of one in one-hundred-thousandth normal free acid or alkali, and this would have no disruptive action on the serum proteins, although much less than this would produce great changes in their physico-chemical aggregation, leading to important consequences which will presently be described.

Finally, similar results would be obtained by the addition of weak organic acids, such as acetic or lactic, only apparently more exaggerated still because of the incomplete hydrogen ionization of these acids which constitutes the difference between so-called weak and strong acids; this would result in the colour being changed more slowly, and the slowing down would be exaggerated in the presence of the amphoteric proteins.

The example cited by Professor Bayliss of the change to acid colour of neutral red in serum on the addition of a little lactic acid does not prove, as he supposes, that the lactic acid is not reacting with the proteins; it only proves that he has brought the reacting system, consisting of serum proteins, sodium bicarbonate, carbonic acid, lactic acid, neutral red, to that point of hydrogen ion concentration at which the coloured indicator swings over to the acid colour. Is this not the whole point of the Friedenthal-Sørensen method of measuring hydrogen ion concentration by means of a series of coloured indicators?

It is not contended that such a high degree of acidosis as that indicated by the colour turning point of methyl orange is compatible with life, but that in the reacting system protein + alkali + carbonic acid there is a marked difference from the system alkali + carbonic acid only,

and that the influence of the protein is a profound and vital one, so that life is impossible in its absence. If the presence of protein increases the titration value up to the methyl orange point from three-fold to five-fold, surely in the first part of the range nearer to neutrality the presence of protein capable of combining with either acid or alkali cannot be without effect. In such a complex system alkaline carbonates are not first neutralized to exhaustion and then serum-proteins, but both are neutralized together, and this is demonstrated in a way of practical importance by the change in the osmotic properties of the proteins as neutralization proceeds.

The effects of protein, both of plasma and of corpuscles, in combining with alkali and so protecting against invasion of neutrality, is shown by subjecting whole blood to a vacuum. This older method of determining the blood gases taught many lessons which seem likely to be forgotten in the rush of new methods. Without the addition of any acid, exposure of warm blood to a vacuum removes the whole of the carbon dioxide free and combined. What becomes of the free alkali and alkaline reserve? This is a question of fundamental importance in clinical conditions of acidosis, such as those enumerated earlier in this paper. If the whole of the carbon dioxide be pumped off from blood the denudation of carbonic acid does not even stop at the stage of normal sodium carbonate, it passes right over into the stage of free caustic alkali, unless the alkali set free can find something in the blood to combine with, and if the figures for the amount of sodium bicarbonate given by Van Slyke and Cullen be accepted, there would be an alkalinity due to caustic soda of 0.03 normal, and so a hydrogen ion concentration shown experimentally by about $10^{-12.5}$ instead of, as actually the case, of about 10^{-7} . Of course, free alkali is not formed, the alkali combines with the proteins of the blood which yield the protective action required, and this same protective action is often exerted *in vivo*, especially when a man or animal ascends a mountain height or undertakes aviation at high altitudes. The same effect in lessened degree happens with plasma alone, and a sample of serum left in an evacuated desiccator with an absorbent for carbonic acid will lose the whole of its free and combined carbonic acid eventually, and all the alkali will pass into combination with serum proteins; this is shown by the curves of Van Slyke and Cullen¹⁹ for amounts of combined carbonic acid corresponding to varying concentrations of free carbonic acid. Theoretically this should be the case also with solutions of sodium bicarbonate, but the important work of Buckmaster²⁰ clearly demonstrates that it would require a geological epoch of time for its consummation.

All this goes to show what an important part proteins, both of corpuscles and plasma, take in the regulation of acidosis, and it is to be feared that neglect of this function and a too great simplification of the problem by attempting to reduce it to one of sodium bicarbonate solutions only is leading the minds of observers away from living conditions and restricting the outlook. It is quite a wrong idea, for example, to suppose that acidosis can be determined by acidifying the blood and determining the amount of carbon dioxide that can be pumped off in a vacuum; such determinations may give absolutely misleading results if the cause of the defect of carbonic acid be not regarded. If a sample of the blood of an aviator at a high altitude be taken and analysed, it will be found that the amount of carbon dioxide in it is much reduced, but the aviator is not suffering from acidosis: he is suffering from just the reverse condition—namely, too much alkali in his blood, which his proteins are being taxed to accommodate, and this vicious condition is being increased by the excessive respiration caused by diminished oxygen pressure. Under such conditions increase of carbon dioxide in the diluted air does not lead to hyperpnoea, for animals (rabbits) have been kept by Edie and Moore in air diluted to an oxygen content of 5 per cent. for over forty hours, a dilution at which in the open air life would be impossible, and these animals breathed quite quietly, showing no other evil effects than drowsiness.

It follows that carbon dioxide pumped off from acidified serum need not previously have been present as sodium bicarbonate; indeed, sodium bicarbonate added to a protein solution no longer exists as simple bicarbonate, but only as a factor in a complex mixture and modified by the balance in that mixture.

The next point criticized is the statement that there exists a union between the serum proteins and the neutral salts, and that the salt content is regulated in this manner, and evidence is asked for as to the existence of such compounds between crystalloids and colloids. A full account of the matter will be found in my paper in the Italian *Archivio di fisiologia* (vol. vii, 1909, p. 519); there is only space here to say that the type of union concerned is one of very common occurrence in colloidal chemistry, and especially in bio-chemistry. There is no rupture of atomic linkages, but a combination between molecules with formation of more complex "solution-aggregates." It has been shown by Moore and Roaf that the action of anaesthetics is due to such molecular union. Similar unions take place in the formation of protoplasm and the attachment to it of atomically saturated organic nutrients, in the union of water of crystallization to crystalloids, in complex salt formation, and in the union of single molecules in fifties and sixties, as, for example, in the case of silicic acid or ferric oxide, to form colloids.

It is no evidence against the union of crystalloids with colloids to state that depression of freezing point is unaffected or that the attached electrolytes still conduct. The sodium and chlorine ions of a solution of sodium chloride conduct electricity and the depression of freezing point is doubled by the ionization, but it would surely be an error to state that sodium ions and chlorine ions are therefore not in a condition of chemical union. There is a sufficient degree of freedom of movement of the ions to admit of conduction of electricity, and for each ion to take up independent atomic motion and give rise to osmotic pressure, but the sodium ions and chlorine ions cannot be massively separated without great expenditure of energy and neutralization of ionic charges, and to this extent there is union between sodium ions and chlorine ions. Similar freedom exists between sodium and chlorine ions united to a colloidal complex such as a solution-aggregate of serum-protein, but they are satellites of that solution-aggregate and cannot be separated from it without expenditure of energy.

The evidence for union between colloid and crystalloid in the blood may be briefly enumerated as follows: (1) The colloids are dissolved or precipitated by variations in the concentration of crystalloids in the plasma. It is difficult to conceive how this can occur without interaction. Thus fibrinogen and globulin are precipitated when sodium chloride is dialyzed away and the precipitates redissolve in dilute sodium chloride solution. All the proteins of the plasma are precipitated when the concentration of neutral-salts is increased. (2) The colloids of plasma are most difficultly separable from crystalloids, as has been emphasized by Professor Bayliss²¹ himself, who points out that a pure protein entirely free from crystalloid has probably never been prepared. Also, in this process, as separation becomes more complete, the physico-chemical properties of the colloids change, sometimes reversibly, sometimes irreversibly. (3) Selective affinity for crystalloids is exhibited amongst the proteins of the body; for example, the tissue cells and blood corpuscles unite with potassium and phosphatic ions, and the plasma proteins with sodium and chlorine ions. (4) As shown by Moore and Parker,²² Moore and Roaf,²³ and confirmed by Lillie²⁴ and others, even small variations in concentration of dissolved crystalloids lead to marked changes in the osmotic pressure of the proteins. Bayliss,²⁵ in confirming and extending the work of Moore and Roaf on osmotic pressure of solutions of gelatin and of gum acacia, found that presence of sodium chloride decreased the higher pressure obtaining in water solution down to a pressure somewhat lower than that of the serum-proteins, in saline solution isotonic with blood. This change is due to increased aggregation or incipient precipitation following on union of crystalloid and colloid. It is this power of retaining salts in the circulation along with the osmotic pressure still remaining over in presence of the saline which confers on transfused blood, or solutions of gelatin or gum, that advantage which they possess over saline alone as injections for combating shock. Saline alone under shock conditions has no colloid to bind it and is promptly removed from the circulation. The same fate would befall the normal saline of the plasma were it not united to the proteins. (5) Finally, the titration figure of the serum to acid and alkali

between the two limits of slow variation in hydrogen ion concentration gives a range of between 0.15 and 0.16 normal; outside this limit the combining powers of the proteins are saturated and ionic concentrations change rapidly. Measurements of depression of freezing point show that the total molecular concentration of the inorganic salts amounts to 0.155 normal. Taking all the evidence together there can be little doubt that this is no chance coincidence, but rather that the inorganic salt-content of the plasma is regulated by the combining powers of the proteins, and that renal excretion and thirst are employed to maintain concentration at this level.

In conclusion, attention may be drawn to the observation of Roaf and Adamson²⁶ that at the neutral point the osmotic pressure of the serum-proteins falls to zero, because of the important effects this must produce in surgical shock and allied conditions. The degree of acidosis experimentally observed in shock often lies at that level which would be produced by the amount of acid added by these observers when they found that the osmotic pressure had dropped to zero.

The amount of acid required to produce zero osmotic pressure in serum cannot be described as strong acid action, the addition was only 0.02 normal, and more caused the pressure to rise again. At this level the plasma can still easily hold 20 to 30 c.cm. per cent. of carbon dioxide, and such amounts are often found in severe acidosis and in shock. The condition of acidosis in the blood has been shown by Van Slyke and Cullen to be reflected on to the tissue cells, as is indeed naturally to be expected. Hence a similar variation in the state of aggregation of protein can be induced in the cells approaching incipient coagulation, and a fall in osmotic properties and change in chemical affinities will accompany this. In this alteration nerve cells, cardiac muscle cells, and the involuntary muscle cells of the blood vessels will all be involved. The chemical alterations in the blood and tissue cells produce a generally relaxed condition.

When it is realized that the reacting system is not a simple one of neutral inorganic salts and sodium bicarbonate only, but one with complex proteins of plasma, tissue cells, pathological products of metabolism, feeble organic acids, and toxins of bacteria, it becomes easier to understand that pathological acidosis is not a simple thing easily produced in a healthy animal by injections of acid, or equally easily combated by injection of sodium bicarbonate. Also, it becomes clearer that different types of acidosis exist, due to different kinds of disturbances of the balance of neutrality, that these types will show different clinical signs, and the disturbing pathological chemical substances can only be removed in different ways. For example, Van Slyke and Cullen injected into a large animal which would possess a calculated blood volume of one litre, no less than 75 c.cm. of normal sulphuric acid, an amount sufficient to neutralize all the alkali in the blood of the animal nearly three times over, and yet after forty minutes the alkalinity had only fallen to about half its normal value, and the animal soon showed recovery. Such an experiment by no means copies the conditions of acidosis, from surgical shock, wound infection, or irritative gases, where the whole circulatory and nervous systems are probably vitiated by absorbed organic poisons of acidic nature, and where the blood proteins are not united to an acid such as sulphuric, which can readily be neutralized by ammonia or fixed alkaline bases, so setting free again the proteins in unaltered condition, but to organic acids and toxins of quite different orders of affinity. It is also to be remembered that these toxic substances are continually being produced and that there is a competition between this pathological production on the one hand and oxidation, neutralization, and elimination on the other. If the latter processes do not keep the upper hand, the vitiation of the cells and of the entire circulation and excretory systems which must follow as a consequence will determine the result against the struggling organism.

The realization of the factors involved gives some indications for treatment in addition to alkalinization, such as removal of causes of acid production by dieting, rest, and diminution of oxidations by warmth and sleep, removal of blood containing toxins and its replacement preferably by

blood or serum, failing this by injections of gum solutions or salines containing alkali, and stimulation of excretion by all available channels.

REFERENCES.

- ¹ *Proc. Roy. Soc.*, vol. B, lxxvii, 1905, p. 102; *Bio-chem. Journ.*, vol. i, 1906, pp. 88 and 383; vol. iii, 1908, p. 279. ² *BRITISH MEDICAL JOURNAL*, 1918, ii, p. 78. ³ *Journ. of Physiol.*, vol. xxxii, 1905, p. 225. ⁴ *The Respiratory Function of the Blood*, Appendix III, p. 316, and *Proc. Physiol. Soc.*, January, 1914. ⁵ *BRITISH MEDICAL JOURNAL*, 1917, and *Journ. of Physiol.*, vol. li, 1917, p. 380. ⁶ *Amer. Journ. of Physiol.*, 1908-1910, and *Journ. Amer. Med. Assoc.*, vol. lxix, 1917, p. 965. ⁷ *Annals of Surgery*, vol. lxii, 1915, p. 262. ⁸ *Amer. Journ. of Med. Sci.*, vol. clxiii, 1917, pp. 90-99. ⁹ *Journ. Amer. Med. Assoc.*, vol. lxxviii, 1917, p. 1393. ¹⁰ *Surgery, Gynaecology, and Obstetrics*, vol. xxv, 1917, p. 23. ¹¹ *Lancet*, 1917, vol. i, p. 8. ¹² *Comptes rendus Acad.*, vol. cxxxi, 1900, p. 293. ¹³ *C. R. de trav. du Laboratoire de Carlsberg*, vol. xlii, 1917, p. 1. ¹⁴ *Amer. Journ. of Physiol.*, vol. xv, 1906, pp. 257 and 271; vol. xviii, 1907, p. 250; vol. xxi, 1908, p. 427. ¹⁵ *Bio-chem. Journ.*, vol. i, 1906, p. 286 et seq. ¹⁶ *Bio-chem. Journ.*, vol. i, 1906, p. 297. ¹⁷ *Beitr. z. chem. Physiol. u. Path.*, vol. iii, 1903, p. 528. ¹⁸ *Schafer's Textbook of Physiology*, vol. i, p. 153. ¹⁹ *Journ. of Biol. Chem.*, vol. xxx, 1917, p. 289. ²⁰ *Proc. Physiol. Soc.*, 1918. ²¹ *Bio-chem. Journ.*, vol. i, 1906, p. 175. ²² *Amer. Journ. of Physiol.*, vol. vii, 1902, p. 261. ²³ *Bio-chem. Journ.*, vol. ii, 1906, p. 34. ²⁴ *Amer. Journ. of Physiol.*, vol. xx, 1907, p. 127. ²⁵ *Proc. Roy. Soc.*, vol. B, lxxxix, 1916, p. 25. ²⁶ *Bio-chem. Journ.*, vol. iii, 1908, p. 422.

THE TREATMENT OF EPILEPSY BY COLLOSOLO PALLADIUM.

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For some time I have been using the different collosole preparations in the treatment of furunculosis, seborrhoea, acne rosacea, eczema, etc., and can fully verify the excellent results already stated by Sir Malcolm Morris, Mr. McDonagh, and others, in the *BRITISH MEDICAL JOURNAL*.

A study of the interpretation of the chemio-therapeutic action of the various collosoles led me to believe that, given a suitable collosole, epilepsy should respond to its treatment. Without at the moment entering into my reasons, collosole palladium suggested itself to me as a preparation which should give good results.*

I therefore took twenty-three typical epileptics for systematic treatment and carefully examined the night and day records of their fits for the past four months, during which they had been under my own personal observation. Having, therefore, a sound basis to work upon, I injected each patient intramuscularly with 0.5 c.cm. of "pallamine" at intervals of three days. So far the results have been most marked and encouraging. To cite four cases:

Case 1.—H. G., male, aged 45, suffering from epilepsy of a doubtful traumatic history, had an average of at least four fits weekly. These fits were of a very violent nature, the convulsive stage lasting on occasions for an hour, followed by stupor, confusion, and excitement. Three injections were given as stated above. Since the injections only one fit has occurred in a fortnight, and that of a mild nature, lasting only 30 seconds. The patient feels greatly improved in his general health, is less morose, more conversant, expressing himself more lucidly, and is very grateful for the treatment.

Case 2.—M. A. L., female, aged 53, an epileptic of thirty years' standing, with a fit average of six per week, these being of a very violent nature. Since injection, three weeks ago, no fit has occurred, but she has had a few slight sensations. She is now placid, well behaved, and much better in every way.

Case 3.—M. A., female, aged 16, congenital epilepsy. Her fits at times, owing to their extreme frequency, were uncountable. She seldom had less than three or four a day. Since injection, three weeks ago, only four fits have occurred, of a mild nature, and of short duration.

Case 4.—W. H., female, aged 29, had a fit of a very violent nature at fairly regular intervals of three days. The first injection was given fourteen days ago, and to the time of writing no fit has occurred. She is much brighter, greatly improved in health, and has now great hopes of being discharged from the institution recovered.

It is an interesting fact that in two cases 1 c.cm. of collosole manganese was injected as a stimulant after the injections of "pallamine." In both cases a fit resulted.

Generally most of the patients who have been treated have greatly improved. The nurses and attendants have noticed a marked difference in their general behaviour, a

* Colloid palladium (pallamine) can be purchased from Crookes' Collosoles Ltd., 50, Elgin Crescent, W.11.

great diminution in the frequency and severity of the fits, and say that their work in the epileptic wards is lightened to a large extent.

The results so far obtained from this treatment have been so encouraging, in fact, have so far exceeded my expectations, that I hasten to bring the matter before the profession in the hope that others will give this form of treatment a trial, and find great benefit to the epileptic ensuing therefrom.

I am still keeping careful records, and hope that at some future date I may be able to show further results.

Memoranda: MEDICAL, SURGICAL, OBSTETRICAL.

THE NIGHTCAP FOR INSOMNIA.

WHILE the treatment of insomnia in any individual case must depend upon a correct estimation of the particular causes in that case, attention to details likely to assist in wooing sleep must always have precedence over drugs.

From this point of view the wearing of a nightcap takes precedence over the drinking of one. Did our grandfathers and grandmothers think, believe, or know from experience that the wearing of a nightcap encouraged sleep? How did this article come into such prevalent use in olden times? We are not entitled to suppose that the older generation wore it from vanity or foolishness, but rather to presume that it had knowledge and experience on its side, and had found that it encouraged sleep thereby.

This view is supported by war-time experience of the knitted Balaclava helmet and knitted cap comforter. That the feet should be warm in bed is recognized as necessary for sound unbroken sleep, but that warmth of the head may be soothing and sleep-winning is not sufficiently recognized at present in civil practice. The war cap comforter is well named. Those who use it at night in cold weather know its soothing virtues in dug-outs, shacks, huts, brick-floored billets, and such similar resting places.

The use and benefit of this accessory might be extended to civilians suffering from insomnia not of gross organic origin. In addition to its soothing sleep-promoting warmth the cap comforter can be used to decrease the intensity of sense impressions from light and sound, encouraging sleep and lessening the chance of its unnecessary interruption, particularly in the early morning.

It is recognized that light and fresh air purify the bedroom atmosphere and make sleep thereby more wholesome and refreshing. A drawn blind, to a large extent, excludes these. The open window, however, admits the full intensity of sounds from outside and daylight tends to waken the sleeper too early. The cap comforter is used to diminish these sensory excitants. The lower part, folded to a treble thickness, is brought over the ears and eyes. The sleeper then has all the benefit of the fresh air and purifying light without the disadvantage of sensory excitation of the eyes and ears. Extraneous sounds are greatly diminished in intensity and darkness is over the eyes. Thus two real objections sometimes raised by a patient to the open, blindless, curtainless bedroom window are removed. For those who know its value the cap comforter is a potent nightcap.

There is another war-time practice prevalent among soldiers for inducing sleep. As, prior to sleeping, the bird puts its head under its wing, and other animals curl up and thereby lessen the respiratory exchange, so, not infrequently, the soldier pulls his blanket completely over his head to facilitate sleep. He thus obtains increased head warmth, diminished sensory excitation, and a narcotic effect from rebreathing his own carbonic acid. While this practice cannot be recommended as giving healthy sleep it does decidedly promote sleep. As would be expected, such sleep is not so refreshing as fresh air sleep, and the man is often slow to waken and in wakening passes through a stupid, confused phase, resembling that of one coming out of a brief anaesthetic state. This practice is most useful where sleep is being prevented by coldness of the body due to wet clothing, wet feet, or insufficiency or wetness of blankets. The heavy sleep gives a welcome escape for the time being from the many abominations of the war zone.

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