EDINBURGH UNIVERSITY CLUB OF
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THE CLINICAL ESTIMATION
OF THE
ALKALINITY OF THE BLOOD:
A CRITICISM AND A COMMENTARY
by
"SCRUTATOR".

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Awarded the Edinburgh University London Club Prize,
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Among the factors which compose the environment of a cell in the human body none, we would suppose, could be of greater importance than the chemical reaction of the fluid medium in which that cell lives. Our sense of the importance of this reaction is increased rather than diminished by the knowledge of the fact ascertained by physiologists that during life this reaction is invariably alkaline in its nature and, indeed, no other would appear to be compatible with the continued existence of the cell. It must, therefore, be of the first importance for physiologists to ascertain what are the variations in the degree of this alkalinity which are compatible with health for pathologists to inform themselves to what extent variations outside this health limit either themselves produce, or are produced by the morbid processes of disease. Notwithstanding this seeming importance, however, the subject is one which has received but scant attention in comparison with that which has been devoted to the study of the variations in the cellular elements of the blood and in some of the chief constituents of these cell elements, e.g. Haemoglobin.
This defect is specially observable in English scientific literature, Jeffries\(^1\) being the only English writer who has treated the subject at all fully. The present writer has, during the last 5 years, devoted considerable attention to the variations in the alkalinity of the blood in disease and to the methods by which these can be clinically estimated and has taken occasion to make himself thoroughly acquainted with the continental literature bearing upon the subject. He has come to certain conclusions regarding these methods and the results which they have already afforded or are likely in the future to afford. The present essay is intended as a criticism upon these methods and a commentary upon their results.

**Initial difficulties.**

On attempting to estimate the alkalinity of the blood by the ordinary chemical method employed for other fluids, i.e. by adding an acid titration till a neutral reaction is reached, we are confronted by certain initial difficulties. These are due in part to the physical characters of the blood and in part to its chemical composition. The fact that the blood is a highly albuminous fluid forbids the employment

\(^1\) Jeffries, Reaction of the Blood. Boston Medical and Surgical Journal. Vol.120.
Initial difficulties. 

(continued)

Physical

of a mineral acid, being also of a somewhat thick consistency
the through admixture of the acid demands some trouble, and
when this has been done the red colour of the blood is apt
to interfere with the precise determination of the end reaction.
Further the blood is not homogeneous but consists of particles,
the corpuscles, suspended in a fluid, the plasma. The deter-
mination of the alkalinity of the whole blood must include both
these elements. Now by the separation of the corpuscles it
has been found that these contain more alkali than the serum
(Landois) - any method, therefore, which does not ensure
thorough breaking down of the corpuscles, with consequent libera-
tion of the alkaline salts therein contained, cannot give
accurate results. The peculiar chemical composition of the
blood presents even greater difficulties. It must be borne
in mind that the blood is not by any means a simple chemical
solution, but, on the contrary, consists of a highly complex
mixture of salts in various and varying combinations. Of
these, two, the bi-carbonate of soda and di-sodic phosphate
($Na_2HPO_4$) are chiefly responsible for the alkaline reaction.

But in both of these salts there is still present an atom
of hydrogen replaceable by metal. Yet both react as alkaline
to ordinary reagents. Hence the curious paradox which has
been emphasised by Drouin\textsuperscript{2)} that the blood is chemically an \textbf{acid} but reacts as an alkaline solution to ordinary colour reagents, and he has estimated this 'acidity' by a special method of titration and finds that it fluctuates just as the alkalinity does. Apart from this the coloured reagent added, or employed, to show when the neutral point is reached, has a considerable influence upon the result obtained. Thus we find that monobasic salts of phosphoric acid are \textbf{acid} to litmus but neutral to phkaleine, dibasic salts of the same acid are alkaline to litmus but neutral to phkaleine. Now as such salts are normally present in the blood the result we obtain will obviously depend on whether we employ litmus or phkaleine as indicator. In addition to this \(\text{CO}_2\) is always present in the blood, but when liberated by the addition of another acid it escapes as a gas and affects litmus feebly if at all. In the case of disordic phosphate on the other hand the phosphoric acid liberated is able to act upon litmus as acid. Hence a blood the alkalinity of which is chiefly due to phosphate of soda will give an apparently lower alkalinity than one in which the alkalinity is chiefly due to the bi-carbonate.

\textsuperscript{2)} Drouin, \textit{Hemo alcalimetrie et hemo acidimetrie}, These, Paris, 1892.
Nor does this exhaust the list of difficulties. It has been specially insisted upon by Meyer\(^3\) that we have no right arbitrarily to select a certain reagent e.g. litmus and exclude from the category of acids all substances which fail to give a red reaction with it. Thus some alcohols, some amide acids and some amides are chemically acids but do not react as such to litmus, and these may be present in the blood. Some of the higher fatty acids, also, when liberated are insoluble in water and therefore cannot affect the litmus.

When we consider these objections we might at first be tempted to abandon any attempt to gauge the alkalinity of the blood as in the nature of things impossible. The physical difficulties, however, can as we shall see, be overcome by suitable methods, while as regards the chemical objections it must be said that many of them are rather theoretical than practical. For although it be true that blood is in one sense an 'acid' fluid in that it contains many salts with replaceable hydrogen atoms, yet we find that these salts which give what we commonly understand by an alkaline reaction predominate greatly over the others. Now what we wish to obtain is a

\(^3\)Meyer, Archiv. f. exper. Path. u Pharmak. XVII, 1883.
quantitative - not a qualitative result. That is to say, the Blood reacting to litmus as ordinary alkaline solutions do, we can ascertain not; perhaps, to the presence or absence of what particular substances fluctuations in this alkalinity are due, but yet to what degree the fluctuations themselves occur. Our results will be comparative, not absolute. The mixture of different substances in solution in the Blood always yielding a balance in favour of alkalinity to litmus, our methods should be able to show us whether this balance is disturbed, and if so, whether in the direction of increase or diminution. The substances which while chemically acids do not react so to litmus are not likely to be present in the blood in such quantity as materially to affect our results.

Let us ask then, what methods we have at our disposal for estimating the total alkalinity of the Blood, and we shall confine ourselves to methods of clinical applicability. Obviously we cannot justly demand from such a method too great accuracy. Like all clinical methods it must needs be more or less of a compromise between accuracy and simplicity, but it should be able to inform us of fluctuations in the degree of alkalinity of the Blood with as much accuracy as we can
inform ourselves of fluctuations in the number of corpuscles or in the amount of their Haemoglobin. We shall now proceed to consider the available methods and how they answer the requirements above set forth. Luntz (Centralblatt für die Med. Wissenschaften, 1867) was one of the first to estimate the alkalinity of the blood. He employed titration by means of Phosphoric Acid. This method demanded too much blood to be available for clinical purposes, and the same criticism applies to the method of Lassar (Archiv f. die Gesammte Physiol. Bd. 68) who employed tartaric acid instead of Phosphoric Acid. Liebreich (Bepichte der deutsch.chem. Gesellschaft i.48 (1868) devised a method for showing the alkaline reaction of the blood by means of plates of plaster of Paris impregnated with litmus. When a drop of blood was placed upon the plate the plasma soaked in and changed the litmus to blue - the corpuscles remaining on the surface where they could be wiped off without obscuring the result. Obviously such a method really gave only the alkalinity of the plasma and not of the total blood, as the red corpuscles, which as we have seen are rich in alkali, were not broken down. Besides it could not show to what degree alkalinity of the plasma existed. After this
we find Renzi\textsuperscript{4} employing this method to estimate variations in the alkalinity of the blood in disease, but as he was guided solely by the intensity of the blue colour produced by different bloods his results are certainly not accurate. Lépine\textsuperscript{5} and Canard\textsuperscript{6} were the first who made extensive observations in man using the titration method but employing comparatively large quantities of blood. It was not until ten years ago that Landois\textsuperscript{7} introduced a method which required only easily obtainable quantities of blood. As this is the type of titration method now in use it deserves a word of description. The principle of the method consists in preventing coagulation of the blood by a neutral salt solution while all the alkali present is neutralised by titration with tartaric acid, litmus paper being employed to show the end reaction. Solution of sulphate of soda is accordingly prepared and to this a solution of tartaric acid is added in graduated amounts. Thus solution I. will contain $\frac{10}{100}$ acid
\begin{equation*}
\begin{array}{c}
\text{II.} \\
\text{III.} \\
\text{IV.}
\end{array}
\end{equation*}
and so on up to $\frac{100}{10}$. Equal quantities of one of these solutions and of blood are sucked up into a fine pipette mixed in a watch glass and reaction tested with

\textsuperscript{4} Renzi, Virchow's Archiv. Bd. 102, 1888. \\
\textsuperscript{5} Lépine, Gazette Médicale, 1879. \\
\textsuperscript{6} Canard, Thèse, Paris, 1878. \\
\textsuperscript{7} Landois, Real Encyclopédie, 1885.
sensitive litmus paper — if still alkaline the next strongest solution is taken and so on till result is neutral. This method has been largely employed by von Jaksch\(^8\), who drew the blood with cupping glasses, and by Peiper\(^9\) who found the latter unnecessary. It has found its most recent advocate in Drouin\(^10\) whose thesis constitutes the most comprehensive monograph on the alkalinity of the blood which has yet appeared.

He has slightly modified the method of Landois, using a normal oxalic acid solution to mix with the sulphate of soda solution. With a dropper he places in the first glass 1 drop acid and 9 of sulphate, the 2nd. receives 2 of acid and 8 of sulphate and so on up to the 10th. An equal amount of blood is then added to each glass and rapidly titrated delicate litmus paper being used to determine in which glass the reaction of the mixture is neutral. This method is on the whole simpler than the original one of Landois and quite as accurate.

Now all these methods have the drawback of being somewhat elaborate and demanding for their proper application a considerable amount of blood, of apparatus and of practice and a large amount of time. It was, therefore, much to be desired

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\(^10\) Drouin, op. cit.
that a simpler method might be found. Such a method Haycraft and Williamson believed to have discovered in 1888 and described it in the Proceedings of the Royal Society of Edinburgh for that year. Since then this method has received favourable notice in various standard works dealing with clinical methods (see von Jaksch's Clinical Diagnosis 3rd. edition 1894 and Finlayson's Clinical Manual) and is advised for employment on account of its simplicity. The present writer accordingly started his observations by the use of this method, he employed it in nearly 500 cases of disease and believes that he is able to demonstrate conclusively that it is entirely unreliable and undeserving of any place in clinical methods of investigation. In order to make clear the reasons for this condemnation a brief description of the method must first be given.

The method of Haycraft and Williamson depends on the fact that if a drop of blood be placed upon the surface of a neutral glazed litmus paper the glaze prevents the corpuscles of the blood from entering the interstices of the paper, while the plasma is able to soak in, and on wiping away the drop the blue colour due to the alkalinity of the plasma is distinctly seen - unobscured by the red colour of the corpuscles.
The fact that the alkalinity of the blood could be demonstrated in this manner was pointed out some years ago by Huntz and by Schafer. It occurred to Haycraft and Williamson that by treating litmus papers with different strengths of a solution of acid and then glazing the papers thus obtained, one would get a series of graduated strength one of which would just be neutralised by the alkalinity of normal blood - all the papers more strongly acid than this would remain unaltered on wiping away the drop of blood, while all the less acid papers would exhibit a blue reaction which would be the more strongly marked the less acid the paper. The method of preparing the papers is described in detail in the original communication of the authors above referred to.

This method seems at first sight to be a great advance upon the titration procedures. It has the undoubted merit of simplicity and can be carried out with great rapidity. Haycraft stated that by its means he had found the reaction of the blood to vary as greatly as that of the urinex). Hence it would seem to answer every requirement. The writer started his investigations with the use of this method under the belief that it really possessed all these advantages.

Specimens of acidified glazed litmus papers prepared for testing alkalinity of Blood according to Method of Haycraft & Williamson. No. 1 = most acid paper.
He prepared papers according to the general directions of Haycraft and Williamson. He found it simpler, however, to get neutral litmus papers ready glazed and to treat these with different strengths of acid - the glaze is not thereby sufficiently removed to prevent the blue colour left on wiping away the drop of blood from being distinctly seen. Sulphuric acid was used to impregnate the papers - a series of 10 being prepared. The first, or strongest paper was soaked in a normal solution of sulphuric acid, No. II was soaked in \( \left( \frac{N}{2} \right) \text{H}_2 \text{SO}_4 \), No. III in \( \left( \frac{N}{3} \right) \text{H}_2 \text{SO}_4 \) and so on up to \( \frac{N}{9} \) which was the weakest of the series. (Examples of the papers employed have been pasted in on opposite side of the paper). It was found by experiment that normal blood reacted to \( \frac{N}{5} \) all the papers above this were unaffected while all below gave a blue reaction. By placing the papers in a row in a small letter clip they could be dipped rapidly into a drop of blood, the drops wiped in the same order and the highest paper which gave a distinct blue colour noted. This represents the alkalinity of that particular specimen of blood, the standard having been already determined by experiments with normal blood. Of course the results afforded could only be approximate as there is a
<table>
<thead>
<tr>
<th>Disease</th>
<th>Name</th>
<th>Age</th>
<th>Paper</th>
<th>Remarks.</th>
</tr>
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<tbody>
<tr>
<td>Chlorosis</td>
<td>Annie Law</td>
<td>8</td>
<td>I</td>
<td>Hb. 32%o Reds normal.</td>
</tr>
<tr>
<td>Simple Anaemia</td>
<td>Jas. Feeney</td>
<td>9</td>
<td>I</td>
<td>Reds 3000,000 Hb. 35%o</td>
</tr>
<tr>
<td>Chorea</td>
<td>R. Lamb</td>
<td>11</td>
<td>IV</td>
<td>Sod. Salicyl grs. x t.i.d.</td>
</tr>
<tr>
<td>Measles</td>
<td>Sarah Mc.L.</td>
<td>8</td>
<td>III</td>
<td>Temp. 103 F.</td>
</tr>
<tr>
<td>Rickets</td>
<td>Alex. Dunsmuir</td>
<td>2½</td>
<td>IV</td>
<td>No anaemia.</td>
</tr>
<tr>
<td>Leucocytomaemia</td>
<td>Mary R.</td>
<td>35</td>
<td>III</td>
<td>Whites: Reds:1:10 - Reds 4000,000</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>John Smith</td>
<td>9½</td>
<td>IV</td>
<td>Just after crisis.</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Mrs. Young</td>
<td>54</td>
<td>IV</td>
<td>Bile acids and pigment in urine.</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Lizzie</td>
<td>22</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Uraemia</td>
<td>Elizabeth R.</td>
<td>18</td>
<td>IV</td>
<td>During convulsions.</td>
</tr>
<tr>
<td>Diabetic Coma</td>
<td>Jas. B.</td>
<td>24</td>
<td>VI</td>
<td>Comatose for 1 hr. Blood V dark &amp; thick</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Jas. Mc.K.</td>
<td>65</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

Specimen page of observations made by Haycraft and Williamson's method, showing apparent increase of alkalinity in anaemias. N.B. Normal Blood reacts to Papers III - IV. No.1 most strongly acid.
often, apparently excessively above the normal. Now if there be one fact on which all those who have employed the titration method are agreed it is this - that in anaemia the alkalinity of the blood is below the normal and often, indeed, to a very marked extent. (see von Jaksch, Peiper and Drowin, already quoted). Only in a few cases of pure chlorosis, i.e. of reduction of the haemoglobin only, was the alkalinity found - as estimated by titration - to be normal or in excess. How, then, is this contradiction in the results yielded by the two methods to be explained? Why should the alkalinity of the blood in anaemia as estimated by Haycraft and Williamson's method be found to be notably increased, while when estimated by Landois' method it is found to be notably diminished? Both results cannot be correct. One or other method must be faulty, must be, therefore, unreliable and to be rejected. Which is it to be?

It might at first be asserted that the results of the two methods are not comparable because while the titration methods destroy the red corpuscles so liberating the alkali which they contain, in Haycraft's method the red corpuscles are obviously left upon the surface of the glazed paper and
Results of the 2 methods not strictly comparable.

This will not suffice as an explanation.

Is explanation to be sought in the diffusibility of the blood?

never come into contact with the limus at all. Haycraft's method, therefore, can only give the alkalinity of the plasma. Landois' gives that of the blood as a whole. This objection is perfectly justifiable but it will not meet the special difficulty we have to deal with - and for this reason - It has been shown that the alkalinity of the corpuscles of the blood is greater than that of the serum (Landois), hence, titration methods which liberate the alkali from the corpuscles should give a higher alkalinity of the blood examined than a method which like that of Haycraft and Williamson gives the alkalinity of the plasma alone. But our difficulty was to show why, in anaemia the very reverse of this occurs, why, that is, Haycraft's method should show a higher alkalinity than Landois.

In searching for another explanation it struck us that the watery condition of the blood in anaemia might be at the root of the mystery. Obviously a watery alkaline fluid will diffuse through the glaze on the surface of Haycraft's papers more rapidly than a more viscid one. More of the acid will thus be neutralised in a given time and the watery fluid will appear more alkaline than the more viscid fluid.
even although the actual amount of alkali contained in both be identical. This would at once explain why an anaemic blood should, when examined by the glazed paper method be found to be apparently more alkaline than a blood which is normal. It remained to put this explanation to the test of experiment.

And first one had to determine whether, say, a 'normal' acid paper was, or was not, just neutralised by a normal alkali solution, an $\frac{N}{2}$ acid by an $\frac{N}{2}$ alkali and so on. Haycraft believed apparently that this was so for he says if the blood in any given case just reacts to $\frac{N}{X}$ acid we know that this will just be neutralised by $\frac{N}{X}$ alkali, and as we know the amount, say of Na OH, contained in such an alkaline solution we can easily estimate the amount of alkali contained in the blood in terms of NaOH. Then he makes the significant addition.

"This is, perhaps, not absolutely true, for probably the blood plasma does not percolate so readily into the litmus paper as does a watery solution of an alkali in this case, however, the error will be uniform". (quoted in von Jaksch's Clin. Diagnosis) Professor Haycraft has evidently never put the question to the experimental test. Had he done so he would doubtless have found, as the writer has done, that, so far from, say, an $\frac{N}{1}$
alkali solution just neutralising a paper impregnated with \( \frac{N}{1} \) acid solution, such a paper gives a distinctly blue reaction even with an \( \frac{N}{150} \) alkali solution! If, now, one takes a comparatively viscous alkaline solution, and for this purpose the writer employed a solution of caustic soda in glycerine - one finds that the result is quite different. If, for example, one adds to 50cc neutral glycerine 1cc normal soda solution it will be found to react to about paper No. III. If 20cc of distilled water be then added to this alkalised glycerine and the papers again tested it will be found that a more acid paper will now react, that is, although the solution is really more dilute than before yet apparently it is more alkaline, a paradox which is evidently to be explained only by the more rapid and thorough percolation into the paper of the more watery solution. We think it unnecessary to give further proof of the great influence which the consistency of the fluid exerts as a factor in determining to which paper it will react, is, we think necessary.

To return now to the blood. It will be at once evident in the light of the above experiments, that the diffusive power of the drop as determined by its greater or less viscosity, is a much more potent factor in determining to which of
Haycraft and Williamson's papers it will react, than is the greater or lesser amount of alkali which it contains. Inasmuch as this viscosity is an inconstant and indeterminable quantity we are compelled reluctantly to conclude that the method is deprived of all reliability and therefore of all practical utility and should no longer be recommended in works of clinical reference. We have given the evidence on which we have come to this conclusion in some detail as we considered this just when employed in the critical discussion of the work of a physiologist of some repute.

Therefore driven back to the titration method.

This method, which promised so much having failed us, we are driven back upon the employment for the clinical determination of the alkalinity of the blood, as one of the titration methods, that is, practically, the method of Landois or Drouin's modification of it. It must be realised, however, that this method gives the alkalinity of the blood as a whole, not that of the plasma only. Now we do not know that the amount of alkali contained in the corpuscles is likely to be of much importance to the tissues generally which only come into direct contact with the plasma. Hence it does not tell us that which we specially wanted to know, i.e. the degree of
Potentialities of the titration method and its limitation.

Alkalinity of the fluid medium in which the cells are bathed. Nor is this all. The titration method will only give proper results, even as regards the total alkalinity of the blood, if properly carried out. It has been known ever since the alkalinity of the blood first began to be investigated, that the alkalinity diminished rapidly after the blood is withdrawn from the vessels, probably owing to the production of a form of lactic acid during clotting. In order to obviate this source of fallacy it has hitherto been supposed to be necessary to carry out the titration as rapidly as possible so as to ascertain the alkalinity before any acid has had time to form. Those who do this seem to forget that the blood is mixed with sulphate of soda solution with the express object of preventing coagulation. Further, Loewy11 has shown that unless the blood be titrated slowly and at the body temperature all the red corpuscles are not broken down and the total alkalinity is therefore not detected, and he contends that previous results have given too low an estimate - in some cases not much above that of the serum alone - owing to all the red corpuscles not having been attacked. Titration, therefore, can only tell us definitely what is the alkalinity of the blood as a whole.

Estimate of value of the titration method.

and not how much of this is due to alkali contained in the corpuscles and how much to alkalies dissolved in the plasma and further, it can only give us reliable information even upon this one point when carried out with the precautions urged by Loewy, i.e. when performed slowly at the body temperature.

We may turn now to the second part of our subject - the consideration of the results which the above method of estimating the alkalinity of the blood has afforded. Before drawing any conclusions as to the alterations of the alkalinity due to disease we must of course make ourselves acquainted with the variations which occur under physiological conditions. Now the first point we would desire to emphasise regarding the alkalinity of healthy blood is its great constancy. This has been found by every method and the writer was early impressed by it in his investigations. Quantitatively, the alkalinity of healthy blood is about equal to that of 370 mg. NaOH per 100cc.

This constancy is the more remarkable when one reflects upon the varying amount of alkali which must constantly be entering the blood stream. The only circumstances in which it is appreciably altered are during the ingestion of food and after severe muscular work. The alkalinity is considerably increased

Remarkable constancy of alkalinity

Physiological variations.
Physiological variations. (continued)

Physiological variations. in the former condition, decreased as the result of the latter. The increase after meals is synchronous with the appearance of the "alkaline tide" in the urine and the latter is to be regarded as the expression and result of the former. The increase of the alkalinity is probably to be explained in large part at least, by the absorption of considerable quantities of alkaline salts from the food. In part, however, it may be due to the discharge into the circulation of sodium carbonate or bi-carbonate resulting from the production of hydrochloric acid in the secreting cells of the stomach from sodium chloride — the hypothesis advanced long ago by Belice Jones. The fact of the existence of this periodical increase of alkalinity makes it necessary to see that observations on the same case should be made at the same time in relation to food, otherwise the results might be fallacious.

After work.

The effect of severe muscular work is to cause a fall in the alkalinity of the blood, this being probably due to the production of considerable quantities of lactic acid by the metabolism of the muscles.

Pathological variations.

Turning our attention now to the condition of the blood in disease we find that the constancy above referred to is
Pathological variations. (continued)

Constant maintained. 

Reduction much commoner than increase.

Many diseased have no influence.

maintained in a remarkable manner. There are comparatively few diseases in which the alkalinity of the blood is appreciably altered. The balance of alkalinity therefore is not easily disturbed. By what mechanism this balance is maintained we know not; but this we know, that it is a remarkably perfect mechanism. Whenever the alkalinity rises much above the mean, the excess appears to be promptly excreted by the kidney. In the reverse direction, however, the mechanism does not seem to work so well. Considerable quantities of acid products can accumulate in the blood without being got rid of. Hence reduction of alkalinity is very much more frequently found in disease than increase. One may say, indeed, that an increased alkalinity of the blood is, with perhaps one exception, never found as the result of disease. Now there are many morbid conditions in which one would not expect a priori to find any alteration in the alkalinity of the blood and this expectation is usually found to be justified. There are others, however in which from what we already know of their pathology some such alteration might naturally be looked for. Amongst the latter are (1) all diseases associated with profound alterations of the general metabolism, e.g. all fevers, (2) all diseases
Many diseases have no influence. (continued) of the blood itself, (3) some special toxic states e.g. uraemia, jaundice and advanced diabetes, (4) some so called 'diathetic' conditions e.g. gout and rheumatism. Now as a matter of fact, as far as our observations have hitherto gone, the above list includes practically all the diseases in which any marked alteration in the alkalinity of the blood has been found to occur. We shall consider briefly each group individually.

Effect of Fever.

(1) Speaking generally one may say of fever as a process that it is accompanied by a diminution in the alkalinity of the blood. This diminution is very constant, but not invariable, and is found to be roughly proportionate to the height of the fever but not to its duration. It is most probably occasioned by the entrance into the circulation of imperfectly oxidised katabolic products of an acid nature, which are laid hold of by the alkaline salts in the blood and so neutralised. We do not know, however, that any of the general symptoms of fever can be ascribed to this diminished alkalinity, nor that it would be at all advisable to make it the basis of any special line of treatment. For the tissues it is a choice of two evils. Since the acid products cannot apparently be at once eliminated it is better that they should be...
neutralised although the reduction in the alkalinity of the blood is, per se, unfavourable to tissue vitality. It has been shown by Castellino and Cavazzani\(^2\) that alkaline liquids stimulate the protoplasmic movements of leucocytes while liquids poor in alkali seem to render them torpid and it is interesting to collate with this the further fact observed by Fodor\(^3\) that an increased alkalinity of the blood artificially produced renders animals much more resistant to organisms. The bearing of these observations upon the pathology of fever is obvious.

\(^2\) Castellino and Cavazzani, Gazz. degli Ospitale 1895.
\(^3\) Fodor, Centralbl. f. Bakter. u. Parasitik. February 1895.
increased (Peiper) this being the only form of anaemia not accompanied by a lessened alkalinity, von Jaksch\(^1^4\) has found that in anaemia there is an increased amount of uric acid present in the blood. He attributes this to deficient oxidation of the tissues. This is, doubtless, another cause of the diminished alkalinity. On the other hand Spiro\(^\text{15}\) has shown that lactic acid is present in the blood in leucocythaemia.

It is also possible that in anaemia the blood is usually more watery than normal, the saline constituents being reduced just as the cellular elements are. Here again we would point out that the diminished alkalinity of the blood cannot be made a reason for the administration of alkaline remedies in anaemia. Iron and Arsenic are both drugs which tend to reduce the alkalinity of the blood, yet the utility of both in anaemia is undoubted and the mineral acids are probably more helpful than alkales.

(3) In all the toxic conditions mentioned above, the alkalinity is also diminished. In jaundice this is probably to be attributed to the presence of bile acids in the blood.

In anaemia reduction occurs often to a marked extent and this


Taxaemias (continued)

Causes of reduction in some toxaemias.

is the more noticeable as venal disease is not found per se to lead to any reduction of the alkali of the blood. Its presence is an additional argument, were one needed, against the ammonia theory of uraemia, but to what toxic substance it is due is unknown. In diabetes the alkalinity tends to be low but is always specially reduced if coma supervenes. Its occurrence is to be accounted for by the entrance into the blood of oxy-butyric acid. It is worthy of remark that some clinicians e.g. Naunyn, administer alkaline carbonates to their diabetic patients as a matter of routine and in fact as a food, with the object of keeping up the alkalinity of the blood to the normal standard.

(4) We come finally to certain "diathetic" conditions in which the investigation of the alkalinity of the blood is of peculiar interest.

We refer to gout and rheumatism. In the former the alkalinity of the blood is stated to be more reduced than in any other disease. We have had no opportunity of observing a case ourselves but this is just what the known presence of excess of uric acid in the blood would lead us to expect. On the other hand the old 'acid theory' of acute rheumatism
Gout
Rheumatism.

Effect of Drugs.

lends to the determination of the alkalinity of the blood in that disease a peculiar interest. Is the alkalinity reduced? The reply is definitely and almost unanimously in the negative. Peiper, von Jaksch and Droben have all failed to find any reduction and with their results the observations of the present writer agree. This is confirmatory of the results of special analyses. Garrod (Reynolds' System, 1st. edition) having failed to find any uric acid in the blood in acute rheumatism while Salomon has failed to demonstrate the presence of lactic acid. In chronic articular rheumatism and in rheumatic arthritis the alkalinity would appear to be sometimes reduced but this may be due to accompanying anaemia.

We may refer lastly to the effect of drugs on the reaction of the blood. These bring out very clearly the existence of the regulating mechanism. It has been found almost impossible to affect permanently the reaction of the blood by the administration of alkaline or acid substances by the mouth. Hoffmann fed pigeons on substances yielding only an acid ash but found that alkalies were retained in order to form bases with the acids in the blood. This occurs even when more acid is administered than would suffice to neutralise
all the alkali in the body Lassar\textsuperscript{16} obtained only slight effects by the administration of even large quantities of acids, of alkalies, and his results have been confirmed by those of other observers. A few of the so called 'alteratives' such as phosphorus and arsenic have been found to produce some diminution in the alkalinity probably by lessening tissue oxidation. In carbonic oxide poisoning a considerable reduction occurs from the same reason and in this case, the presence of considerable quantities of lactic acid in the blood has been demonstrated (Araki). Our comparative inability by means of drugs to influence the reaction of the blood is remarkable and instructive although therapeutically rather disappointing. We may, in closing, briefly summarise the results of our investigation. We have seen that the clinical determination of the alkalinity of the blood is rendered difficult alike by physical and by chemical considerations. That the existing methods have been devised with the object of surmounting these difficulties. That these methods are for practical purposes only two in number, the titration method (Landois) and the glazed litmus paper method (Haycraft and

Summary

(continued)

Williamson) we believe that we have been able to show that the second of these two methods is worthless, and for this reason— that the reaction it yields is very largely dependent upon the viscosity of the blood examined i.e. upon a factor of extreme inconstancy. Of this we claim to have furnished practical and experimental proof, and would therefore urge that the method should be discarded and its recommendation discontinued. That there is therefore available for the clinical determination of the alkalinity of the blood the titration method alone, troublesome and rather cumbersome though it be. That the results afforded by this method can apply only to the alkalinity of the blood as a whole, and even then, only when the titration is carried out slowly and at the body temperature, are these results reliable. We are thus left in ignorance how much of the alkali in any given case is contained in the blood cells and how much in the plasma.

That the clinical application of this method has brought into prominence one striking fact regarding the alkalinity of the blood—its constancy. That this constancy tends to be maintained both in health and in disease and is apparently the result of a regulating mechanism by which alkali is retained or excreted as required. The
The alterations in disease are practically always in the direction of diminution, induced probably by the entrance of acid substances into the circulation. Thus we have carbonate of lime present in leucocythaemia, poisoning, &c.

Lactic Acid present in leucocythaemia, poisoning, &c.

Uric Acid in gout and in anaemia, oxybutyric acid in diabetes.

That in addition to these conditions the alkalinity is reduced in uraemia, in all febrile conditions, in all anaemias with the exception of chlorosis, in which the alkalinity is normal or even increased. The reasons for the reduction in these different diseases we briefly discussed. That with these exceptions, morbid processes like those which are physiological are not accompanied by appreciable alterations in the alkalinity of the blood. Lastly, we saw that, owing in large measure to the existence of the regulating mechanism already referred to, we are practically unable materially to influence the reaction of the blood by the administration of drugs.

As the number of available observations by different observers is now fairly large and covers nearly every known disease, one is entitled to conclude that not much more will be made out by existing methods, and on reviewing the practical
Concluding remarks (continued)

results of the information acquired one is bound to confess that they are rather meagre. These results certainly throw side lights, even if of a negative character, on some pathological questions; but as regards direct clinical bearing it is, we think, evident that the information to be derived from the estimation of the alkalinity of the blood in any given case is hardly commensurate with the expenditure of time and trouble which that estimation entails.