OBSERVATIONS UPON THE VARIATIONS OF THE ALKALINITY OF THE BLOOD AND THE ACIDITY OF THE URINE IN SCARLET FEVER

by

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P R E F A C E.

My original idea in commencing the series of observations which I now present as a thesis was to ascertain:

(1) If there was any relationship or ratio between the variations in the alkalinity of the blood and the acidity of the urine.

(2) To test the theory that the true re-action of the blood must be acid, because the urine, a fluid derived from it, is acid.

(3) To test the theory that the alkalinity of the blood was lessened by pathogenic micro-organisms, and those diseases associated with a febrile movement.

(4) Whether any indications as to treatment could be obtained.

For the purposes of (1) and (2) it is true that different and opposite qualities are being compared, but it seemed reasonable to assume that a considerable variation in the re-action of one fluid might be re-flected by an alteration in the other, as they are intimately related to one another.

The cases of disease most suitable for making these observations upon besides normal persons seemed to be those suffering from Septicaemia, but it would be difficult to obtain a sufficient number of observations in a reasonable time. I, therefore, chose Scarlet Fever, as pyrexia is usually associated with this disease, and the researches of Horder [1] and others have shown that micro-organisms are circulating in the blood of persons suffering from the disease.

I have first of all considered:

(1) The re-action of the blood.

(2) The re-action of the urine;

then given the results of my observations with certain notes upon them, and finally the conclusions drawn therefrom.

THE REACTION OF THE BLOOD.

Under normal conditions the reaction of the blood is alkaline owing chiefly to the presence of sodium carbonate and disodium phosphate. There are also present acid phosphates, but their acidity is masked by the presence of an excess of bicarbonates. The physiologists all agree that blood is alkaline, and that the slightest degree of acidity is fatal.

On the other hand there are several arguments in favour of the blood being acid, notably that it will absorb $C.O_2$ which is only absorbed in an acid medium. No one however has yet practically demonstrated this acidity, while the alkalinity is easily demonstrated with good litmus paper.

In health by the perfect mechanism of the emunctory organs the normal balance of blood alkalinity is constantly maintained in spite of the entrance of acids into the blood whether by the ingestion of acid substances or by their production within the system, for the hyperacidity from such causes is promptly removed from the blood by the action of the kidneys, the skin and the lungs. It is probable, that the tendency to acidity is partly neutralized by the ammonium salts generated from proteid foods and

also by the action of the liver. The blood alkalinity may be transiently increased by administering an alkali internally or by enema, the latter method having the more pronounced effect according to Orlowsky.(2)

Increased alkalinity goes hand in hand with increased antidotal action of the blood against bacterial infection. (Da Costa & others) Von Rigler(3) found that the blood contained more acid than the blood serum. He found that the action of micro-organisms of which he tested eleven pathogenic varieties in sixty-three experiments was constantly in the direction of a decreased alkalinity affecting both the total blood and the serum. The reduction in alkalinity was greatest in cases of fatal infections though not necessarily in the rapidly fatal forms.

Most observers agree that as a rule the alkalinity of the blood is perceptibly lowered in those diseases associated with a febrile movement, but no definite relation between the intensity of the pyrexia and the degree of lessened alkalinity has been established.

Desevres(4) however, has drawn attention to the fact that in the early stages of acute diseases the alkalinity is either normal or somewhat increased, and in the majority of instances it becomes perceptibly diminished during convalescence. In chronic diseases it is usually decreased if the duration of the disease has been of long standing.

The rat has a high alkalinity of the blood and body fluids, and is immune to anthrax, but susceptible to plague.

Clinically the degree of alkalinity is determined by ascertaining the amount of sodium hydroxide which is exactly neutralized by 100 c/c of blood, the result being expressed usually in milligrams of Na O H per 100 c/c of blood. The figures given by different investigators as representing the normal alkalinity range within the widest limits, chiefly in consequence of the many different methods by which such data were obtained. In view of these marked discrepancies, the alkalinity figures of different workers are in no sense comparable unless they are based upon precisely similar methods of investigation pursued with identical technic.

Kraus	162 - 232
Tunty and Lehmann	240
Orlowsky	240 - 267
Dare	266
Strauss	300
Lowy	449
Engel	479 - 533

Hutchinson(2) and subsequently A.Lowy showed the inadequateness of the older methods of estimation, especially when opaque blood was employed.

The methods of alkalinity estimation devised by Landois, Liebreich, by Haycroft and Williamson, by Wright and by Kraus are not well adapted to routine blood work, being either too complicated and elaborate for such a purpose, or too inaccurate.

In Wright's method the blood serum only is used and in Landois opaque blood. Both methods use litmus as the indicator, and this gives rise to uncertainty owing to the well-known peculiarity of litmus pigment to react amphoterically to mixtures of both alkaline phosphates (primary and secondary) contained in the blood.

With the titration method now generally admitted to furnish fairly accurate results, appreciably higher figures are obtained with laked whole blood than with serum alone, since by the former method the alkalinity of all the plasma and cellular elements is estimated, while by the latter the influence of the corpuscles is entirely eliminated.

A. Lumière, L. Lumière and H. Barbier[5] have investigated the value of the titration method for determining the alkalescence of the blood, and point out that it gives uncertain results because when any acid is added in excess, and the excess then determined by titration with an alkali, a certain amount of the acid remains in combination with organic bases, etc.

Of the different methods two are most suited for clinical use, Dare's and Engel's.

Dare by means of a specially designed apparatus sucks up 15 mg. of blood and dilutes it with distilled water. A tartaric acid mixture is then slowly added until the absorption bands of Oxyhæmoglobin disappear from the blood mixture, and are replaced by those of Methæmoglobin, the test being made with a Browning Spectroscope. The amount of acid solution is noted on the scale of the pipette and the alkalinity can be computed from a given table.

With this instrument the figure for normal blood is 266 mgm. of Na OH per 100 c/c of blood.

Objections to Dare's Method[6] :

The author assumes that the disappearance of the haemoglobin spectrum is coincident with neutralization. This has not been conclusively proved, and furthermore the spectroscopic changes dependent upon variations in reaction are slow in their appearance.

Lowy uses a titration method, and lacmoid paper as the indicator.

ENGEL'S METHOD.

Finger blood obtained by a deep puncture so as to afford a good sized drop is sucked up in a special pipette to the mark 0·05 immediately after which

distilled water is similarly drawn up the lumen of the tube until the mixture of blood and water fills the bulbous portion of the tube and reaches 5.0 in the constricted portion beyond. Twist rapidly while sucking up to mix. As soon as the dilution has been made the pipette should be shaken for a minute or so until the mixture becomes of a uniform 'laky' tint, which indicates that all the haemoglobin has been dissolved from the corpuscular stroma. The contents of the pipette are blown out into a glass cylinder, and $\frac{1}{75}$ normal solution of tartaric acid added from a burette, graduated in $\frac{1}{20}$ c/c, stir between each drop. Test from time to time with lacmoid paper, the titration being continued until the reaction recognised as a bright red halo which forms around the edge of the drop, is obtained. Note number of drops used. Usually in normal blood 9 -11 are required to give the reaction.

The estimate of the total alkalinity of the blood is made by multiplying by the figure 53·3 the number of drops required. 10 : a (drops) :: 533.0 : x. The result thus obtained is expressed in milligrams of Na OH per 100 c/c of blood.

Equivalent weight of tartaric acid is 75

and sodium hydrate 40

that is 1 litre of $\frac{1}{75}$ normal tartaric acid solution saturates $\frac{40}{75}$ = 533 mgm. of Na OH.

Objections to Lowy's and Engel's methods[6]

The relations of lacmoid pigment to mixtures of primary and secondary alkaline phosphates should be more carefully examined before any judgement is formed as to the reliability of Lowy's or Engel's method. Lowy's and Engel's results correspond. Waldvogel with Salkowski's method obtained similar results.

As Engel's Method seemed the most free from objections, and the most convenient clinical method, I adopted it in a slightly modified form. An objection to all clinical methods of estimating the blood alkalinity is that such small quantities of blood are obtainable that the results must be uncertain. We are dealing with very weak solutions, and I found that with the lacmoid paper I obtained, 3 drops of $\frac{N}{75}$ tartaric Acid were required to make 5 c/c of distilled water give an acid reaction. Special sensitive litmus paper never gave definite results.

Phenolphthalein I attempted to use by making a faintly alkaline solution so that by artificial light drops of it upon a porcelain plate had about the same colour as the diluted blood. When the blood was acidified a drop mixed with a drop of the indicator produced a very definite decolourization. Unfortunately phenolphthalein will at times react acid to blood. When it did not do so the results obtained

with it were usually half those obtained with lacmoid.

My results agreed with Engel so far that I found 9-10 drops were required with normal blood to give a faint pink reaction to the lacmoid paper, but deducting the three drops referred to above 6-7 drops or 319-373 mgms. of Na OH were required to neutralise 100 c/c of blood.

ACIDITY OF THE URINE.

Normal urine has an acid reaction, due not to free acid, but to acid salts, especially di-hydrogen sodium phosphate, H_2 Na PO_4. At times the re-action may be amphoteric. This is due to the presence of the acid di-hydrogen phosphate and the alkaline disoduim phosphate in a definite relationship of such a nature that each salt is capable of exerting its influence upon the indicator without interference with the other. This is only possible provided the acid salt is not present in too great an excess.

Specimens of urine voided at different times of the day react differently, a variation depending largely upon the phenomena of digestion. During digestion the secretion of HCl by the stomach diminishes the acidity of the urine which may even become alkaline. The nature of the food will alter the re-action of the urine. A vegetable diet being rich in bases, or a liberal consumption of wine or of fruit may cause the excretion of an alkaline urine; the alkalinity is occasioned by the fact that the organic acids become oxydised in the body to alkaline carbonates. On the other hand a diet rich in proteid or meat being poor in bases will intensify the acid re-action, because acids, especially H_2 SO_4 result from oxidation of proteid in the organism.

If from any cause the food bases are insufficient to prevent the excessive acidity some of the ammonia which is split off from the tissue-protein supplements them and neutralises the excess. Dreser (Hoffmeister's Beitrage z. chem Physiol. 1905) denies that the acidity of urine is due to a mixture of monohydric and dihydric phosphates, he believes that along with the dihydric salt, a free acid - phosphoric or organic - is present in urine.

By the administration of the alkalies, their carbonates or their vegetable-acid salts such as citrate or acetate of potash, the urine can readily be made to yield an alkaline reaction. Citrates and acetates of the fixed alkalies are converted by the tissues into carbonates which appear in the urine and render it alkaline. Citrate and acetate of ammonia however, do not render the urine alkaline as the ammonium carbonate which is formed is hydrolysed by the liver cells and is transformed into urea before it reaches the kidneys.

Whilst it is easy to make the urine alkaline by means of saline drugs, it is difficult when patients habitually secrete alkaline urine to reverse the action and make it acid, acid medicines have but little power in this direction. Hutchison has obtained good results from frequent half drachm doses

of the acid phosphate of sodium. (B.M.J. 1903). The reaction of individual specimens of urine varies.

The quantitative estimation of the reaction by means of acidemetry or alkalinity is accomplished by titration. Certain objections have been constantly raised in reference to the possibility of titrating the acidity of the urine, and these objections have been considered in Nageli's[7] experiemnts upon this subject. These objections arise from the fact that theorectically the end reactions of the titration of phosphoric acid are never distinct and not always so even from a practical standpoint. So long as the chemist gives us nothing better however we are forced to use these methods in practice and Nageli has shown that it is possible to obtain approximate values for the acidity of the urine by means of titration.

At first sight it seems impossible to compare the state of the urine on one day with another unless a twenty-four specimen is taken. The objection to a twenty-four specimen is that decomposition alters the acidity, and that it is also unduly altered by the food and exertion during the day.

M. H. Joulie has evolved a method by which observations on the acidity of the urine may be compared with each other.

Am extensive series of observations have been made by him and J. Nicolaidi of Paris.

Joulie recommends that the estimation should be done not upon a twenty-four hours specimen, but upon a specimen passed in the early morning as this is a truer type of the normal urine and is uninfluenced by food and exertion.

The estimation of the specific gravity must always be performed at the same temperature or a collection made for any variation.

No coloured indicators are advised nor required.

He uses a solution of sucrate of lime:- $Ca(OH)_2$ 10 grammes, sugar 20 gmes. distilled water 1 litre. After mixing the clear solution is syphoned off, and standaridised with an acid solution of known strength.

This solution with monobasic acids and litmus or phenolphthalein gives the same results as caustic soda.

filtered urine which contains
With Phosphoric Acid it forms at first monohydric-calcium-phosphate and the mixture remains clear. When triple phosphates are being formed the mixture becomes turbid and the titrating is stopped as soon as this cloud persists. It appears as a fine haze easy to appreciate. The quantity of lime solution required is noted and its strength being known the acidity per litre is calculated.

The result is then divided by the excess of the urinary density over water and multiplied by 100 giving the percentage of total acidity to the solids of the urine.

By this means M. Joulie claims that it is possible to compare urines varying in quantity and quality, and he gives his standard as being between 4 and 5. His arguments are to me convincing, but they require to be produced in full.

He considers that it is also necessary to ascertain the amount that acid phosphates contribute to this acidity and though for my main purpose this is unimportant from the point of view of treatment, it is very necessary.

The estimation of the amount of phosphates is done by the usual uranium nitrate method using cochineal as an indicator and the result worked out in gmes. per litre is, as in the preceding estimation, reduced to the amount per cent of the total solids.

By dividing the percentage of total acidity into the percentage of phosphates the percentage of active phosphoric acid is obtained.

If the urine was 1030 S.G. and the total acidity was estimated as 1·25 per litre $\frac{1.25 \times 100}{30} = 4.2$ = the percentage of total acidity to the excess of density. If the urine was 1016 S.G. and the total acidity .75 per litre $\frac{.75 \times 100}{16} = 4.7$, so that what at first sight looks like a wide difference becomes when expressed in this form of ratios only a small amount.

To fully appreciate the system it is necessary to read M. Joulie's full address on the subject with his arguments for and against it. He does not claim to estimate the total acidity as there is no means of doing this, but only what he calls the physiological acidity.

In my estimations I found that both the total acidity and the phosphoric acid varied more than in the cases he observed. My purpose, however, is to compare my results with each other and not with his. My standards for normal agreed with his.

RESULTS OF OBSERVATIONS.

In order to be able to compare a specimen of blood and urine from the same patient, my method was to take the blood late, about the time the patients were being settled up for the night. The urine evacuated about this time was discarded, but so far as possible the next specimen passed was used, as this would be the urine secreted from the blood just after the puncture.

As standards I have decided upon:-

(1) Total alkalinity of the blood 319.8 - 373.1 mgm of Na OH.

(2) Total acidity of urine 4- 5% of the excess of density over water.

(3) Phosphates, total - 8 - 10% do. do.

The first observations upon each case were compared with these standards, and subsequent observations with the preceding one. The results are obtained from the examination of sixty cases, mostly of a severe type.

The summary of all the observations shows that:-

TABLE I.

	Alkalinity of the Blood	Acidity of Urine.	Phosphates Inc.	No Change	Dec.
32%	Increase	Increase	11%	5%	16%
33%	No change	Increase	22%	1%	10%
16.3%	Decrease	Increase	12%		4.3%
11.7%	Increase	Decrease	4%	1.7%	6%
7%	Decrease	Decrease	3%		4%

The amount of alkalinity of the blood was found to range from 212 mgms. to 533 mgms. of Na OH per 100 c/c.

In 32% 29% 33%

it was 371mgms 319mgms 426 or 479 mgms.

The remaining 6% gave figures above or below these, and were rarely encountered.

In 17% only of the cases examined was the estimated blood alkalinity at the commencement of the illness as low as it became during convalescence. The highest alkalinity in uncomplicated cases was reached between the commencement and the twelfth day of disease.

In 66% it was at its highest point when the first observation was taken between the second and fifth day of disease, and while the temperature was still high.

The lowest record was obtained from a convalescent patient who developed a rigor a few hours previously. He was then found to have secondary adenitis of the cervical glands. This condition cleared up quickly without suppuration intervening. At the same time his urinary acidity reached its lowest point.

Generally the most severe cases registered the highest alkalinity of the blood.

When convalescence was established (third to fifth week) the degree of alkalinity was very variable In 50% of the cases it was at its lowest value though this figure in many of the cases had been reached before. In 40% it was at its previous highest value, and in the remainder it was at an intermediate figure.

The effect of complications upon the blood alkalinity was indefinite.

The four most severe cases which were diagnosed as a septic form of Scarlet Fever (but recovered), all showed high alkalinity, and in three gave extreme variations in the acidity of the urine, the difference being as much as 120%.

Neither these nor any other cases showed any definite relation in the variation in the amount of acidity of urine to the variation in the amount of blood alkalinity. One case showing an increase of

80% in the acidity without any alteration in the blood alkalinity.

In all four cases when the convalescence was approaching the alkalinity became less while the acidity increased.

The acidity of the urine was at its lowest observed point (i.e. practically at the apparent normal) in 12% of the cases at the commencement of the disease. Of the remaining 88%, in one sixth of them the acidity reached its highest point at the observation taken within five days of the definite commencement of the disease. In 86% of all the acute cases the urinary acidity was highest between the fifth and fifteenth day and in the most severe cases it was postponed even longer.

Except in the milder cases it did not return to its apparent normal until after the twenty-second day of disease, and until after all symptoms except desqumation had disappeared. Complications invariably delayed the reduction of acidity, and usually increased it. In all the advanced convalescent cases the amount of acidity reached either its lowest point or its apparent normal.

P H O S P H A T E S.

Although in every case the total amount of phosphates was estimated I have not worked out special tables of comparison for them. Their variation from normal was only well marked in 40% of the observations. The greatest frequency of change was shown in the Nephritis cases.

Nearly half the cases showed an increase in the first few days with a return to about normal or below in the second week. About the same number showed the reverse of this.

The proportion of Phosphoric Acid generally varied correspondingly, but the amount of variation was almost always lower.

SCARLATINAL NEPHRITIS.

The results of observations upon eight cases of Scarlatinal Nephritis are given below:

TABLE II.

	Alkalinity of Blood	Acidity of Urine	Phosphates Inc.	Dec.	No Change
40%	Increase	Increase	13%	27%	-
20%	Decrease	Decrease	12%	8%	-
8%	Decrease	increase	8%	-	-
4%	Increase	Decrease	4%	-	-
12%	No Change	increase	12%	-	-
8%	No Change	No Change	4%	-	4%
8%	No Change	Decrease	-	4%	4%

These cases in the acute stages showed very wide variations both in the amount of alkalinity of the blood and the acidity of the urine. The blood alkalinity showed a difference between the highest and lowest estimation of as much as 50% in six of them and the urinary acidity as much as 100% in all except one, and was always 40% above normal even when no blood was present in the urine and only a small amount of albumen. In old standing cases where the amount of albumen present was less than .5 grammes per litre the acidity returned to the neighbourhood of the normal.

On the coagulation time of the blood, estimated by Addis's[9] modification of McGowan's method neither blood alkalinity nor urinary acidity had any relation, but this usually decreased as the amount of albumen decreased.

RESULTS OF OBSERVATIONS UPON SIX CASES OF POST-SCARLATINAL DIPHTHERIA.

Alkalinity of Blood	Acidity of Urine.	Phosphates Inc.	Phosphates Dec.
31% No Change	Increase	20%	11%
21% Increase	Decrease	11%	10%
11% Increase	Increase	11%	-
11% Decrease	Increase	11%	-
5% Decrease	Decrease	-	11%
5% Decrease	No change	5%	-
5% No change	Decrease	-	5%

The above results are too variable and too few to be a reliable guide. These cases showed the widest variations in the alkalinity of the blood, the increase in the highest record upon the lowest on the same case being 50% in all the five cases constantly observed.

In contrast to this they showed the smallest variations in the acidity of the urine of all the cases tested, as this with the exception of one observation never varied much from the normal and the greatest difference was a decrease of 40%

One of the cases gave the highest alkalinity of the blood obtained, 533 mgmes Na OH. He developed very mild attack of mitral regurgitation, but no œdema nor cardiac dilatation. It is however interesting to note that high (but not constant) alkalinity of the blood was found. The acidity of his urine was very constant, a few points above normal, while the blood alkalinity varied from 426 - 533 mgmes, but on the occasion when the blood alkalinity was lowest, 373 mgmes, the urine acidity was highest.

C O N C L U S I O N S.

The results obtained are disappointing and mostly negative.

(1) Table I, page 18 shows that alteration in the strength of the reaction of both fluids in an upward or downward direction was shown in 40% of the observations but this is not a high enough majority to justify the assumption that increased blood alkalinity causes increased urinary acidity nor vice versa, also as already mentioned the change in one fluid was usually not in the least degree proportional to the other.

Only 28% of the observations showed that when the reaction of one fluid increased the other decreased. The reasons mentioned above even more strongly prevent any assumption to be drawn from this.

Finally one third of the estimates showed that the urinary acidity could vary without the reaction of the blood altering.

So far as my observations go no relationship or ratio between the variations in the reactions of the blood and urine can be shown.

(2) The theory that the blood is acid because the urine is acid seems to me to be opposed by my

results shown in Table I. If the blood were acid, increased acidity of the urine would denote increased acidity of the blood and a diminution in the amount of its alkaline constituents capable of estimation, but 40% of the observations show the reverse, while another 33% show that there was no change in the blood.

(3) So far as my observations go the alkalinity of the blood is not lessened by Scarlet Fever, a disease associated with a febrile movement, and in which micro-organisms are frequently found present in the blood. There is rather at the start, or early in the course of the disease, a reactionary alkalinity, see page 18 (next to Table I.)

(4) As to treatment, I regret to say that my observations have not continued over a long enough period to enable me to come to any conclusion. The results in the Diphtheria cases seemed to indicate the giving of acids, and Sulphuric and Phosphoric Acids were tried. The latter seemed to have a decided beneficial effect, but it is necessary to test a series of uncomplicated Diphtheria cases before an opinion can be given.

Salicylate of Sodium and Aspirin in the few cases given caused a marked increase of blood alkalinity and urinary acidity with similar decreases on its withdrawal.

For acute Scarlet Fever the indications obtained seem generally in favour of giving alkalies, but I have not yet put this view sufficiently to the test.

REFERENCES.

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(5) Arch. de Med, Experimen, 1902, XIII, 6, p.791

(6) Sahli's Clinical Diagnosis.

(7) Eur Aciditatsbestimmung des Urines. Zeits. f. Physiol. Chemie, Vo. XXX, pts. 3-5.

(8) L'Acidité Urinaire". Conference faite le 19 Mais, 1901, par M. H. Joulie, Transactions of Pasteur Inst, Paris, or published by Revue Généralé de Chemie Pure et Appliquée, Paris.

(9) Addis, T. Quart. Journal Exper. Physiology, 1908, Vol. I. No.4.

The following books have also been quoted from frequently:

Nothnagel's "Practice of Medicine."

Da Costa's "Haematology."

Sahli's "Clinical Diagnosis."

Mann's, "Physiology and Pathology of the Urine."