ACIDOSIS AND ALKALOSIS
ACIDOSIS AND ALKALOSIS

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PREFACE

DURING recent years the disturbances of acid-base balance have assumed increasing importance. Advances in chemical physiology and biophysics along these lines have thrown a flood of light on many of the phenomena of disease which until comparatively recent times were little understood, and the knowledge acquired in the laboratory can now with profit be employed at the bedside.

The literature has grown enormously so that it is difficult for anyone not engaged in research work on these or kindred subjects to obtain a comprehensive view of the facts upon which the modern ideas are based. This book attempts to give a general survey of the subject and its application to disease, keeping in mind the needs of those not versed in recent chemical physiology. To accomplish this has been a more difficult task than we anticipated, and it has been necessary to steer between the Scylla of simple formulæ and the Charybdis of higher mathematics. We are well aware of many omissions, but we would plead as an excuse our attempt to simplify the subject. For example, we have refrained from entering into a discussion of the acid-base disturbances in pneumonia since this would have entailed a full consideration of the biochemistry of hæmoglobin and would, we feel, have complicated our task unnecessarily. At any rate, this subject has been dealt with by Meakins.
and Davies much more fully than we could have done.

It will be obvious that special attention has been paid to conditions met with in infancy and childhood, since most of our experience has been gained in a children's hospital. This we consider an advantage, as it is in the early years of life that such disturbances have their greatest incidence and significance.

A bibliography in a book of this nature is always a problem. We have not attempted to give the source of all the facts, but have limited our references to certain monographs themselves containing good bibliographies, to some classical contributions and to the papers quoted in the text. We should like to make special mention of the volume on *Quantitative Clinical Chemistry. Interpretations*, by Peters and Van Slyke, of which we have made free use. The source of each figure if not original has been acknowledged in the text, and we should like to express our thanks to the respective authors and publishers for permission to use these figures. We also desire to acknowledge the courtesy of the following journals for permission to use figures and tables taken from some of our own papers: *Archives of Disease in Childhood, Journal of Physiology*, and *Glasgow Medical Journal*.

To Dr. Leonard Findlay, who was Visiting Physician at the Royal Hospital for Sick Children, Glasgow, and Professor of Pædiatrics in the University of Glasgow when we commenced our investigations, we would convey our very best thanks. Not only has he afforded us considerable help by his criticisms and suggestions, but he was responsible for initiating many of the investigations which we have undertaken. To Professor G. B. Fleming we are deeply indebted for
his constant and untiring interest in the preparation of the book and for his many valuable suggestions. To our colleagues, past and present, at the Royal Hospital for Sick Children, Glasgow, we would also express our thanks. We have made free use of their results. To Miss Mary Gardner, who has assisted us in the preparation of the manuscript, index, and diagrams, we tender our sincere thanks for her invaluable co-operation. Finally, we owe a debt of gratitude to the Medical Research Council, from whom we have received personal grants which have allowed us to devote so much time to the study of these problems.

Our cordial thanks are due to the publishers, especially Mr J. McDonald Walker, for their helpfulness in the preparation of the volume.

S. G.
N. M.

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Glasgow,
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CHAPTER I

INTRODUCTION

One of the most remarkable characteristics of the living organism is the constancy at which it maintains the composition of the fluids surrounding the cells. Small changes, too small for our detection, are constantly occurring and being adjusted as part of the ordinary life and activity of the organism. When, however, these changes exceed certain narrow limits, a state of disordered metabolism is set up which is manifested by certain signs and symptoms. These manifestations are not necessarily pathological, but should be looked upon as indications of the body’s effort to control the situation.

The regulation of the acid-base equilibrium is probably one of the most delicately adjusted of the regulating processes. The tissue fluids of the living organism have constantly to be kept in a state of slight alkalinity, and even a moderate departure from the normal may lead to serious interference with the various activities of the tissues. On the other hand, alterations in the metabolism of the tissues themselves have a profound effect on the acid-base balance. Since the observation of Stadelmann in 1888 that “the symptom complex of diabetic coma greatly resembles that of acid intoxication,” evidence has been accumulating which goes to show that a disordered metabolism leading to a disturbance in acid-
base equilibrium is the cause of many morbid conditions, and further, that many of the phenomena in disease are manifestations of the body's activity in preventing a change in the reaction of its fluids.

Normal life cannot be sustained unless the reaction of the body and its fluids is kept practically constant. Metabolic processes, however, lead to the formation of acids such as carbonic and lactic and the diet contains varying amounts of acid and alkali. The digestive juices dispose of some acid (in gastric juice) and some alkali (in bile and pancreatic juice). The net result of all these processes is the production in the body of a great excess of acid over base. It is said that in the course of each twenty-four hours the lungs get rid of the equivalent of 20–40 litres of normal acid (carbonic), and the kidneys of 50–150 c.c. (chloride, sulphate, phosphate). It is clear that even in health adjustments must always be taking place. So delicate are these compensatory measures that changes during health can hardly be detected by the methods at our disposal. Haldane has stressed the point that this regulation of reaction is not merely the maintenance of equilibrium of acid and base: compensatory measures are themselves the result of physiological activity. The manifestations of disturbed acid-base equilibrium should therefore be thought of not merely as evidence of morbid functioning, but as physiological adjustments to alterations in the tissue fluids. Consequently, the proper interpretation of signs and symptoms associated with disturbances in acid-base equilibrium may become a matter of extreme importance. These disturbances are of special importance in the growing child. Not only are they more frequently encountered in infancy and childhood, but
the ability to overcome the upset and to re-establish normal equilibrium is less perfectly developed. It is as if the younger organism lacked practice and experience.

Maintenance of a constant reaction of the blood, however, is much more complicated than the mere regulation of excretion of acids and bases. Respiration and urinary excretion, by which means practically all the acid is got rid of, are influenced by many factors other than the presence of acid substances in the blood. It is well, therefore, to remember that a study of acid-base equilibrium throws light only on one aspect of the problem of disease. Not only are other factors of importance but they generally act and are reacted on by the state of the acid-base equilibrium.

There are two possible deviations of acid-base equilibrium from normal, one where the body is less alkaline than normal (acidosis), and the other, where it is more alkaline than normal (alkalosis). In medical literature the terms acidosis and alkalosis have come to denote not merely physico-chemical changes, but also the associated clinical manifestations such as changes in breathing and urinary excretion. It is, however, wrong to consider acidosis and alkalosis as disease entities. Findlay has likened acidosis to fever as a symptom or sign of disease, and there is much to be said for such a comparison. Both conditions are manifestations of the body’s reaction to pathological processes, and both may act as pathogenic agents. The signs and symptoms by which we recognise these changes mean little in themselves unless we have an understanding of their mode of production and realise that they form part of the body’s adaptation to disease. As L. J. Henderson has remarked, “nothing is more wonderful or instructive than the condition of an
individual who has long been suffering from a progressive disease like chronic nephritis, who is approaching his end but who remains adapted in every part and in every activity to the changed and almost impossible conditions of life.” A knowledge of the adjustments brought into play in disease will enable one to facilitate such adjustments by making conditions as favourable as possible, and thus permit the vis medicatrix naturæ to exert its influence under the most favourable conditions.
CHAPTER II

THE REACTION OF THE BLOOD

Hydrogen-Ion Concentration.—By the term reaction of a solution is meant the degree of acidity or alkalinity. The term acidity is used in two senses, which it is important to differentiate, first as a measure of the total amount of acid, i.e. quantity, and second, as a measure of the strength of acid, i.e. intensity. The total amount of acid in a solution is determined by the amount of base required to make the solution neutral. Thus the amounts of acid present in 20 c.c. of decinormal hydrochloric acid and 20 c.c. of decinormal acetic acid are identical, since exactly the same amount of base (i.e. 80 milligrams of NaOH or 20 c.c. of a decinormal solution) is required to neutralise each. The amount of acid present in any solution is generally expressed as total or titratable acidity. While similar amounts of decinormal hydrochloric and decinormal acetic acids have similar titratable acidities, the strengths of these two acids are very different, hydrochloric acid being seventy times stronger than acetic acid. This is due to the fact that a decinormal solution of hydrochloric acid liberates seventy times more hydrogen ions than a corresponding amount of decinormal acetic acid. The strength or intensity of an acid is therefore synonymous with the concentration of hydrogen ions. Many substances on being dissolved in water break up into their component parts which
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are then known as ions; this process of breaking up is called dissociation. Any substance which, on being dissolved in water, dissociates and yields hydrogen ions in excess is an acid while the liberation of hydroxyl (OH) ions in excess is the characteristic of an alkali. The degree of acidity (intensity) of any solution depends on the relative amounts of free hydrogen ions (H) and free hydroxyl ions (OH) which it contains. Therefore neutrality must be due to an exact balance of H and OH ions. Pure water can be considered a neutral solution since when any of its molecules dissociate they, of necessity, yield equal amounts of hydrogen and hydroxyl ions according to the equation $\text{H}_2\text{O} \leftrightarrow \text{H} + \text{OH}$.

At 22° C., in 10,000,000 litres of distilled water, there is present in the ionic state one gramme of hydrogen ions and one gramme of hydroxyl ions. To put it another way, water is $\frac{1}{10,000,000}$ normal acid, and $\frac{1}{10,000,000}$ normal alkali. The concentration of hydrogen ions (cH) is thus $10^{-7}$ and the concentration of hydroxyl ions (cOH) $10^{-7}$; the product of these is $10^{-14}$.

In any solution, the addition of an acid will increase the hydrogen ions and consequently diminish the hydroxyl ions as the product must remain $10^{-14}$. For example, if acid is added so as to increase the content of hydrogen ions from 1 gramme in 10,000,000 to 1 gramme in 100,000, the concentration of hydrogen ions will become $10^{-5}$, and that of hydroxyl ions $10^{-9}$. Similarly, if an alkali be added, the concentration of hydrogen ions is decreased and that of hydroxyl ions is increased.
The true acidity (intensity) of any solution, then, can best be expressed in terms of the concentration of hydrogen ions, the $cH$; acid solutions have a $cH$ greater than $10^{-7}$, e.g. $10^{-5}$ or $10^{-3}$ and vice versa, for alkaline solutions, e.g. $10^{-9}$ and $10^{-12}$.

**The pH.**—As the use of the negative index figure is inconvenient, Sørensen suggested the logarithmic nomenclature in which the negative logarithm of the $cH$ is given the symbol pH. For example, a tenthousandth normal solution of acid which is completely dissociated has a $cH$ of $10^{-4}$, which represents a pH of 4. The lower the figure representing the pH, the more acid the solution, and the higher the figure, the more alkaline the solution, pH 7 representing neutrality. Table I shows that the pH is really a method of stating the concentration of hydrogen ions.

**Table I**

<table>
<thead>
<tr>
<th>pH.</th>
<th>$cH.$</th>
<th>Gm. of Ionised Hydrogen per Litre of Solution.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$10^{-1}$</td>
<td>0·1</td>
</tr>
<tr>
<td>2</td>
<td>$10^{-2}$</td>
<td>0·01</td>
</tr>
<tr>
<td>6</td>
<td>$10^{-6}$</td>
<td>0·000001</td>
</tr>
<tr>
<td>7</td>
<td>$10^{-7}$</td>
<td>0·0000001</td>
</tr>
<tr>
<td>8</td>
<td>$10^{-8}$</td>
<td>0·000000001</td>
</tr>
<tr>
<td>14</td>
<td>$10^{-14}$</td>
<td>0·00000000000000001</td>
</tr>
</tbody>
</table>

The logarithmic nature of the pH must be emphasised. Small changes in the figure mean great differences in the acidity. Thus a solution with a pH of 7·1 is approximately twice as acid as a solution with
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a pH of 7.4. Figure I shows the diminution in concentration of hydrogen ions as the pH increases from 7.0 to 8.0. The vertical line indicates the degree of acidity, and it is clear that at pH 7.4 the degree of acidity is only half that at pH 7.1. Actually a decrease of 0.1 in pH means an increase in acidity of 25 per cent.

TABLE II
SHOWING DEGREE OF DISSOCIATION OF ACIDS AND BASES.

<table>
<thead>
<tr>
<th>Acids</th>
<th>Percentage Dissociated</th>
<th>Bases</th>
<th>Percentage Dissociated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloric N/10</td>
<td>91.0</td>
<td>Sodium hydroxide N/10</td>
<td>91.0</td>
</tr>
<tr>
<td>Oxalic N/10</td>
<td>50.0</td>
<td>Potassium hydroxide N/10</td>
<td>91.0</td>
</tr>
<tr>
<td>Acetic N/10</td>
<td>1.34</td>
<td>Ammonium hydroxide N/10</td>
<td>0.4</td>
</tr>
<tr>
<td>Carbonic N/10</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acids are classed as weak or strong according to the amount of hydrogen ions liberated: similarly bases are strong when large quantities of hydroxyl ions are present in solution. In other words, the strength of an acid or base is determined by its degree of dissociation or ionisation. Table II shows the degree of ionisation of some common acids and bases.

1 The fact that the degree of acidity of a solution with pH 7.1 is twice that of a solution with pH 7.4 is more apparent when the pH figures are converted into cH.

\[ pH = - \log cH. \]

\[ \therefore - \log cH = 7.1 = 8.0 - 0.9. \]

\[ \therefore \log cH = -7.1 = -8.0 + 0.9. \]

\[ cH = \frac{\text{antilog 0.9}}{\text{antilog 8}} = \frac{7.94}{10^8} = 7.94 \times 10^{-8}. \]

Similarly, with pH 7.4

\[ cH = \frac{\text{antilog 0.6}}{\text{antilog 8}} = \frac{3.98}{10^8} = 3.98 \times 10^{-8}. \]

To convert cH into pH is done by taking the negative value of the logarithm of the cH.

\[ cH = 1.29 \times 10^{-3}. \]

\[ \therefore \quad pH = - \log cH = - \log 1.29 - \log 10^{-3} = -0.1106 + 3 = 2.8894. \]
The reaction of any salt will be acid, neutral or alkaline according to the degree to which the constituent acids and bases are dissociated. Some salts are alkaline (or acid), although they contain no hydroxyl (or hydrogen) ions in their constitution.

**Figure I**

**Showing Relationship of Concentration of Hydrogen Ions (cH) to the pH.**

Thus sodium carbonate (\(\text{Na}_2\text{CO}_3\)) in solution is alkaline in reaction. The sodium carbonate dissociates and the dissociated ions react with the small amount of free hydrogen and hydroxyl ions present in water.

\[
\begin{align*}
\text{Na}_2\text{CO}_3 & \rightleftharpoons 2\text{Na}^+ + \text{CO}_3^2-
\hline 
2\text{H}_2\text{O} & \rightleftharpoons 2\text{OH}^- + 2\text{H}^+
\hline 
\text{H}^+ + \text{CO}_3^- & \rightleftharpoons \text{HCO}_3^-
\end{align*}
\]
H + HCO₃ ⇌ H₂CO₃, which is slightly dissociated (0.17 per cent.)

OH + Na ⇌ NaOH, which is strongly dissociated (91 per cent.).

The end result, therefore, is the production of two substances, H₂CO₃ and NaOH, the first of which is a weakly dissociated acid, and the second a strongly dissociated base. There is thus a great excess of hydroxyl ions, i.e. the reaction is strongly alkaline.

Buffers.—By buffer action one means the resistance to a change in pH shown by certain solutions on the addition of acids or alkalis. The term owes its origin to Sörensen, and its use is restricted now to the meaning here given. Bayliss suggested the use of the word “tampon,” a correct translation of the German word “puffer,” indicating the soaking-up of free hydrogen or hydroxyl ions which takes place. Unfortunately, “puffer” has been wrongly translated into “buffer” in English, and this term is now in universal use. When acids or alkalis are added to distilled water, great variations in the pH of the solution occur. When, however, similar amounts of acids or alkalis are added to a solution containing a buffer, very little change in the pH occurs (Figure II).

A simple example of buffer action is the effect of sodium acetate. The addition of 0.1 c.c. of decinormal HCl to 10 c.c. of pure water changes the pH from 7.0 to 3.0. If to the 10 c.c. of water 0.082 gm. of sodium acetate be added, 9.9 c.c. of decinormal HCl is required before the pH reaches 3.0.

One of the commonest examples of a buffer solution is one containing phosphates. Consider, for instance, two solutions, one, 2 c.c. decinormal HCl diluted to 20 c.c. with distilled water, the other, 20 c.c. of a
1·2 per cent. NaH$_2$PO$_4$ solution. The first has more than one hundred times the pH of the second, but the second solution requires ten times more alkali to make it neutral to phenolphthalein than the first. Furthermore, in the case of the acid, the change will be sudden,

**Figure II**

*Showing the resistance of a buffered solution to change in pH after addition of acid or alkali. The range of buffer activity is in this example from pH 4 to pH 10.*


and with the salt gradual. The second solution is buffered because it contains a weakly ionised or weakly dissociated acid salt, namely, sodium di-hydrogen phosphate. That is to say, it can "soak up" alkali according to the equation,

$$\text{NaH}_2\text{PO}_4 + \text{NaOH} \rightleftharpoons \text{Na}_2\text{HPO}_4 + \text{H}_2\text{O}. $$

Similarly, the alkaline salt can soak up acid,

$$\text{Na}_2\text{HPO}_4 + \text{HCl} \rightleftharpoons \text{NaH}_2\text{PO}_4 + \text{NaCl}. $$
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It is clear, therefore, that the characteristic of a buffering system is its power of minimising changes in degree of acidity (hydrogen-ion concentration) on the addition of strong acid or alkali. This property depends on the substitution of an acid (or alkali) which is weakly dissociated for one which is more strongly dissociated.

The buffering capacity of the salts of the weakly dissociated or ionised acids, such as phosphates, bicarbonate, and hæmoglobin, is used extensively in blood and urine in controlling the reaction of the body. At the pH of the blood, hæmoglobin and the other blood proteins act as weakly dissociated acids. The practical importance of this buffering action of salts and proteins will be appreciated when it is remembered that it is on its buffering capacity that the body primarily depends to withstand sudden fluctuations in the amounts of acid and alkali.

Indicators.—Indicators are substances whose colours depend on the pH of the fluid to which they are added. This property of changing colour at different reactions is dependent upon the behaviour of these substances as weak acids or bases. The change of colour of each indicator takes place within a particular range of pH. Thus Töpfer's reagent (dimethylaminoazobenzene) changes from red to yellow in the pH range 2·9 to 4·0. At a pH below 2·9 it gives a red colour: as the pH increases, the colour gradually changes to yellow until the value of 4·0 is reached, when any further increase in pH will have no influence on the colour. Phenolphthalein changes from colourless to red in the pH range 8·3 to 10·0. Thymol blue, among the commoner indicators, has two ranges, first, from pH 1·2 to 2·8 where the colour changes from red to yellow, and second, from pH 8·0 to 9·6, from yellow
FIGURE III
SHOWING RANGES OF SOME INDICATORS. THE BLACK OR SHADEN AREAS INDICATE THE RANGE OF pH THROUGHOUT WHICH THE INDICATOR CHANGES COLOUR.
(Adapted from: Red, Text-book of Physiology, London.)
to blue. It is clearly necessary in using indicators for the determination of pH to choose one which changes colour at a particular range within which is included the pH of the fluid to be tested. Indicators vary in sensitivity; some are affected by small changes in pH while others require large changes for any effect to be noticed. The first or sensitive group must be used when the solution to be tested contains a substance which is only weakly dissociated, i.e. where the change in concentration of hydrogen ions takes place slowly. Phenolphthalein and phenol-red are examples of this group, whereas litmus (range pH 4.5 (red) to pH 8.0 (blue) is a common indicator which is relatively insensitive, i.e. is only of value when the acids and bases present are strongly dissociated.

PROPERTIES OF BLOOD ON WHICH THE pH DEPENDS

The concentration of the hydrogen ions (cH) in any solution containing an acid and one of the salts of this acid depends on the relative concentrations of the free acid and the salt, i.e. on the ratio \( \frac{[\text{HA}]}{[\text{BA}]} \), A being the acid radicle, and B the basic radicle in the salt.

In 1909, L. J. Henderson formulated the basis of our present knowledge regarding the alkalinity of the blood by stating the ratio given above in terms of the only free acid which is known to exist in the blood stream, namely, carbonic acid (\( \text{H}_2\text{CO}_3 \)) and its salt (\( \text{BHCO}_3 \)). The hydrogen-ion concentration, therefore, is dependent on the ratio of the free to the combined acid, i.e. \( \frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3} \).
THE REACTION OF THE BLOOD

The relationship in the blood of the three variables, free carbonic acid (H$_2$CO$_3$), combined carbonic acid (BHCO$_3$), and concentration of hydrogen ions (cH) is shown by the equation,

\[ cH = k_1 \frac{[H_2CO_3]}{[BHCO_3]} \]

The symbol \( k_1 \) is used to represent the value for the combined dissociation constant of carbonic acid and bicarbonate in the fluid concerned. The explanation of the dissociation constant is one involving principles of physical chemistry which need not be explained here.

**Hasselbalch's Equation.**—In 1916, Hasselbalch modified the above equation to bring it into line with the Sørensen nomenclature, so that

\[ cH = k_1 \frac{[H_2CO_3]}{[BHCO_3]} \]

becomes \( pH = pK_1 + \log \frac{[BHCO_3]}{[H_2CO_3]} \),

where \( pH = \) the negative log of \( cH \),

\[ pK_1 = " " " " k_1 \]

and \( \log \frac{[BHCO_3]}{[H_2CO_3]} = " " " " \frac{[H_2CO_3]}{[BHCO_3]} \).

Recently it has been shown that in addition to the three variables mentioned above there are others, such as free and combined oxygen and plasma chloride concentration. The relationship of all the variables is such that given any two of them the others can be calculated. L. J. Henderson has constructed a nomogram for human blood from which these variables can be read off.

1 The large brackets \([ ]\) signify concentration of the respective substances.
For our purposes, however, it is unnecessary to consider more than the original three—\((cH)\), \((H_2CO_3)\), and \((BHCO_3)\)—and it is proposed for the present to revert to the simpler nomenclature of Henderson as by its means it is easier to appreciate the fundamental principles governing the reaction of the blood.

Normally, the free carbonic acid in the blood amounts to about 8 vol. per cent., and the combined carbonic acid to 60 vol. per cent., thus making the ratio

\[
\frac{H_2CO_3}{BHCO_3} = \frac{3}{60} = \frac{1}{20}.
\]

It must be strongly emphasised that the reaction of the blood will always be normal as long as this ratio is preserved. If the combined carbon dioxide \((BHCO_3)\) be diminished, it may be associated with (1) a corresponding fall in the free carbon dioxide \((H_2CO_3)\), (2) a proportionately smaller fall in the free carbon dioxide, or (3) a proportionately greater fall in the free carbon dioxide. In the first case the ratio remains unchanged, in the second the ratio is increased \((acidosis)\), and in the third case the ratio is decreased \((alkalosis)\) as follows:

\[
\frac{H_2CO_3}{BHCO_3} = \frac{3}{60} = \frac{1}{20} \quad \text{(normal)}
\]

\[
1. \quad \frac{2}{40} = \frac{1}{20} \quad \text{(normal)}
\]

\[
2. \quad \frac{2.5}{40} = \frac{1}{16} \quad \text{(acidosis)}
\]

\[
3. \quad \frac{1.5}{40} = \frac{1}{26.6} \quad \text{(alkalosis)}.
\]
Similarly, a rise in the combined carbon dioxide may be accompanied by (a) a corresponding rise in the free carbon dioxide, (b) a proportionately smaller rise in the free carbon dioxide, or (c) a proportionately greater rise in the free carbon dioxide.

\[
\frac{\text{H}_2\text{CO}_3}{\text{BHCO}_3} = \frac{3}{60} = \frac{1}{20} \quad \text{(normal)}
\]

(a) \[= \frac{4}{80} = \frac{1}{20} \quad \text{(normal)}
\]

(b) \[= \frac{3.5}{80} = \frac{1}{22.8} \quad \text{(alkalosis)}
\]

(c) \[= \frac{5}{80} = \frac{1}{16} \quad \text{(acidosis)}.
\]

Anything which increases the ratio of free carbon dioxide to combined carbon dioxide will result in an acidosis and conversely, anything which diminishes the ratio of free carbon dioxide to combined carbon dioxide will result in an alkalosis.
CHAPTER III

DEFINITION OF TERMS

Acidosis and Alkalosis.—Acidosis may be defined as a condition in which the reaction of the blood is less alkaline than normal, and alkalosis, as a condition in which the blood is more alkaline than normal; the blood is taken as an index of the reaction of the tissues generally. The Medical Research Council's report on "The Acid-Base Equilibrium of the Blood" suggests that these two states should be called acidæmia and alkalæmia respectively. While these terms may be more correct in so far as they refer to the blood which is being examined, they are less comprehensive in that they do not refer to the increase or decrease of the sum total of acid relative to alkali in the body. This is better emphasised by the terms acidosis and alkalosis. Furthermore, acidæmia seems to suggest that the blood actually becomes acid, a condition of affairs that practically never occurs.

Ketosis.—In certain conditions there occurs defective oxidation of the products of fat metabolism resulting in the accumulation in the body of substances known as ketone bodies (acetone, aceto-acetic acid, and beta-hydroxy-butyric acid). Such a condition is known as a ketosis. Much confusion exists regarding the exact meaning of this word ketosis, some authorities reserving its use for the acidosis (when it occurs) produced by the accumulation of ketone bodies. They consider,
for example, that in diabetic coma there is a ketosis, which term implies an acidosis due to ketone bodies. This interpretation may, however, lead to confusion. It is in many cases impossible to say whether the acidosis present is purely the result of the presence of these ketone bodies or of some other acid product of metabolism. In gastro-enteritis, for example, there is present an acidosis, and there are also ketone bodies accumulated in the blood and tissues, as evidenced by their appearance in the urine, but these ketone bodies are not entirely responsible for the acidosis. Furthermore, ketone bodies may appear in the blood and urine in excess in conditions of alkalosis. Therefore, it appears less confusing to use the term ketosis merely to imply the accumulation of ketone substances in the body.

**Ketonæmia and Ketonuria.**—There should be no doubt regarding the meaning and use of these two terms. Ketonæmia (acetonæmia) signifies the presence of abnormal amounts (i.e. exceeding 3·0 mgm. per cent.) of ketone bodies in the blood, and ketonuria (acetonuria) their presence in the urine.

**The Total Carbon Dioxide Content of the Blood.**—This represents the sum of the free carbon dioxide and the combined carbon dioxide in the blood, the limits of normal being 45 to 65 volumes per cent. It tells one nothing about the ratio of the one to the other, and hence gives no information regarding the actual hydrogen-ion concentration. Nevertheless, if interpreted correctly in association with the clinical data, it is of the greatest importance in deciding whether the alkalinity is increased or diminished.

The expression, *carbon dioxide capacity*, which is sometimes used, has a rather different meaning. It
signifies the total volume of carbon dioxide which the blood will hold when equilibrated at the tension of carbon dioxide equivalent to that found in alveolar air. In health, the total carbon dioxide and the carbon dioxide capacity will be for all practical purposes identical, but in conditions where there are disturbances of the acid-base balance there may be significant differences. Normal alveolar air, the gases of which are in equilibrium with those of the blood, has a carbon dioxide tension of approximately 40 mm. Hg. If the tension of alveolar air, for example, is found to be 30 in the subject whose blood is under examination, exposure of his blood to normal alveolar air will slightly increase the amount of carbon dioxide it contains, so that the carbon dioxide capacity will be slightly greater than the total carbon dioxide content of the circulating blood. Conversely, if the tension of carbon dioxide in the alveolar air of the subject be higher than normal, the carbon dioxide capacity may be less than the total carbon dioxide content of the blood.

Alkaline Reserve.—This term, introduced by Van Slyke, represents the volume of carbon dioxide which can be expelled from 100 volumes of blood or blood-plasma which has been equilibrated with normal alveolar air at room temperature and from which the free carbon dioxide has been deducted. It is the carbon dioxide capacity less the free carbon dioxide. The normal limits for the alkaline reserve for blood are 43 to 60 volumes per cent. The expressions, plasma bicarbonate, bicarbonate content, and carbon dioxide combining power have all been used to signify the same thing. The alkaline reserve represents the amount of base left over after all the fixed acids have
been neutralised and gives an index of the amount of base available for any additional acids that may be formed or absorbed. A reduction of the alkaline reserve was at one time regarded as sufficient evidence on which to diagnose acidosis, but although this interpretation is correct in the majority of instances, it may be misleading as the reduced alkaline reserve signifies only a fall in the combined carbon dioxide and tells one nothing about the ratio.

The value for the total carbon dioxide of the plasma depends to some extent on the method by which the plasma has been obtained. When the blood has been exposed to alveolar air (or any gaseous mixture) and the plasma then separated under liquid paraffin to avoid loss of gas, it is known as "true plasma." If the plasma has been first separated from the cells and later exposed to the gaseous mixture, it is known as "separated plasma."

**Fixed Base.**—By this term is meant the alkali of the blood which in contrast to ammonia, is non-volatile. The value for fixed base is always given in terms of a normal solution, either c.c. N/1 solution (milli-equivalent), or c.c. N/10 solution (see Appendix III). Because of the varying atomic weights of the substances comprising the fixed base (sodium, calcium, potassium, and magnesium) it is impossible to express its power of combining with acid in any other way.

**CLASSIFICATION OF DISTURBANCES OF ACID-BASE BALANCE**

In 1921, Van Slyke showed that there are nine possible variations in the relationship of the three variables, cH, H₂CO₃, and BHCO₃, of which only one
is absolutely normal. These have been classified in the following groups:

(1) *Uncompensated Alkali Excess.*—The BHCO₃ is increased, the H₂CO₃ increased to a less extent, and the pH increased.

(2) and (3) *Uncompensated Carbon Dioxide Deficit.*—The H₂CO₃ is decreased, BHCO₃ decreased to a less extent, and the pH increased.
(4) Compensated Alkali Excess.—The BHCO\textsubscript{3} is increased, the H\textsubscript{2}CO\textsubscript{3} is increased to the same extent, and the pH is normal.

(5) Normal Acid-Base Equilibrium.—All three variables are normal.

(6) Compensated Alkali Deficit.—The BHCO\textsubscript{3} is diminished, the H\textsubscript{2}CO\textsubscript{3} diminished to the same extent, and the pH is normal.

(7) and (8) Uncompensated H\textsubscript{2}CO\textsubscript{3} Excess.—The H\textsubscript{2}CO\textsubscript{3} is increased, the BHCO\textsubscript{3} is increased to a less degree, and the pH is diminished.

(9) Uncompensated Alkali Deficit.—The BHCO\textsubscript{3} is diminished, the H\textsubscript{2}CO\textsubscript{3} diminished to a less degree, and the pH is diminished.

From the above classification and Figure IV it becomes apparent that by the term compensated is meant an alteration in the combined carbon dioxide without a change in the pH. For example, one form of compensated acidosis (Group 6) is that in which the bicarbonate is lowered but the pH remains unaltered, while in a further stage of this type of acidosis, the pH is lowered and the condition becomes uncompensated (Group 9). Actually, however, in a compensated acidosis there must be a change in the pH, but it is of a degree which is not detected because the methods of estimation are not delicate enough. Any fall in the BHCO\textsubscript{3} is certainly followed by a corresponding fall in the H\textsubscript{2}CO\textsubscript{3} in an effort to maintain or re-establish acid-base equilibrium. The fall in H\textsubscript{2}CO\textsubscript{3}, however, lags behind the fall in BHCO\textsubscript{3}, and this must produce a slight but certainly definite alteration in the ratio 1 : 20, whether or not it can be detected by present-day chemical methods. If this lag in the fall of the free carbon dioxide did not occur, i.e. if the
ratio were immediately restored exactly to normal but at a lower level of bicarbonate there would be no stimulus for the bicarbonate to return to its previous level. It is the alteration in the ratio which affords a stimulus to the body to expel more acid and to call more alkali into the blood and thus to restore the bicarbonate to its normal level. It has been shown that a rise of 0.2 volume per cent. in the $H_2CO_3$ without change in the $BHCO_3$ is sufficient to double the resting alveolar ventilation. Yet, this acidosis, though sufficient to stimulate the respiratory mechanism to increase its activity by 100 per cent., represents a difference in the pH of only 0.028 (say pH 7.401 to pH 7.378), a change which can just be detected by accurate physico-chemical measurements. For this reason it would appear that the use of the terms compensated and uncompensated is of no particular advantage: the term compensated is so called merely because of the lack of delicacy in the methods employed for the determination of the pH.

**Haldane's Classification.**—The following classification suggested by J. B. S. Haldane seems much more helpful as it gives in each case an indication of the particular procedure employed by the body in the production of the change.

1. **Non-Gaseous Acidosis.**—In this there occurs a primary fall in the combined carbon dioxide ($BHCO_3$) with a secondary fall (but less marked) in the free carbon dioxide ($H_2CO_3$). Thus

\[
\text{Normal} = \frac{3}{60}, \quad \text{total CO}_2 = 63 \text{ vol. per cent.}
\]

\[
\text{Non-gaseous acidosis} = \frac{2.5}{40}, \quad \text{total CO}_2 = 42.5 \text{ vol. per cent.}
\]

This is the classical acidosis, the acid poisoning type
which occurs in diabetic coma, cyclical vomiting, uræmia, gastro-enteritis, salicylate poisoning, and poisoning by any acid salt such as calcium chloride or ammonium chloride. It is characterised by an increase in the cH (fall in pH) and a diminished alkaline reserve. The clinical manifestation of increased respiration is the result of the necessity of getting rid of carbon dioxide.

(2) Gaseous Acidosis.—Here the primary factor is a rise in the free carbon dioxide (\(H_2CO_3\)), with a consequent rise, but to a less degree, in the combined carbon dioxide (\(BHCO_3\)), in an attempt to restore the normal ratio. Thus,

\[
\begin{align*}
\text{Normal} &= \frac{3}{60}, \text{total CO}_2 = 63 \text{ vol. per cent.} \\
\text{Gaseous acidosis} &= \frac{4}{70}, \text{total CO}_2 = 74 \text{ vol. per cent.}
\end{align*}
\]

Here the cH is increased (pH lowered) and the alkaline reserve or total carbon dioxide is also increased. A disturbance of this nature occurs in morphine poisoning where, owing to diminished sensitiveness of the respiratory centre, the subject breathes more slowly and thus conserves free carbon dioxide which provides the necessary increase in stimulation required by the respiratory centre. In other words, the depressed respiratory centre requires a bigger "head" of carbon dioxide to stimulate it.

(3) Non-Gaseous Alkalosis.—There is a rise in the amount of available combined carbon dioxide, followed by a less marked rise in the free carbon dioxide. Thus,

\[
\begin{align*}
\text{Normal} &= \frac{3}{60}, \text{total CO}_2 = 63 \text{ vol. per cent.} \\
\text{Non-gaseous alkalosis} &= \frac{3.5}{80}, \text{total CO}_2 = 83.5 \text{ vol. per cent.}
\end{align*}
\]
ACIDOSIS AND ALKALOSIS

This state occurs in high intestinal obstruction such as pyloric stenosis, in gastric tetany, and in some instances following the administration of sodium bicarbonate where the kidney efficiency is impaired.

### Table III

<table>
<thead>
<tr>
<th>Type of Disturbance</th>
<th>Total CO₂ Content or Alk. Reserve</th>
<th>Occurs in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acidosis</strong>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Due to bicarb. deficit (non-gaseous).</td>
<td>Decreased.</td>
<td>Diabetic coma, cyclical vomiting, gastro-enteritis in infants, dysentery in older children, uremia, salicylate poisoning.</td>
</tr>
<tr>
<td>(a) Compensated (Group 6).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Uncompensated (Group 9).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Due to CO₂ excess (gaseous).</td>
<td>Increased.</td>
<td>Morphine poisoning, emphysema.</td>
</tr>
<tr>
<td>(a) Compensated (Group 4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Uncompensated (Groups 7 and 8).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alkalosis</strong>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Due to bicarb. excess (non-gaseous).</td>
<td>Increased.</td>
<td>Administration of sodium bicarbonate. High intestinal obstruction.</td>
</tr>
<tr>
<td>(a) Compensated (Group 4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Uncompensated (Group 1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Due to CO₂ deficit (gaseous).</td>
<td>Decreased.</td>
<td>Anoxæmic conditions, high altitudes, hyperpnoea.</td>
</tr>
<tr>
<td>(a) Compensated (Group 6).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Uncompensated (Groups 2 and 3).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pH is lowered (pH increased) and the total carbon dioxide is increased. The breathing is slow and shallow, in an effort to conserve the free carbon dioxide and thus to restore the normal ratio.
(4) *Gaseous Alkalosis.*—Here the primary factor is a diminution in the free carbon dioxide followed by a relatively smaller diminution in the combined carbon dioxide. Thus,

\[
\text{Normal } = \frac{3}{60}, \quad \text{total CO}_2 = 63 \text{ vol. per cent.}
\]

\[
\text{Gaseous alkalosis } = \frac{2}{45}, \quad \text{total CO}_2 = 47 \text{ vol. per cent.}
\]

This gaseous alkalosis is seen in conditions where there is "washing out" of the carbon dioxide as in cases of forced over-ventilation or hyperpnœa, which has been observed as a sequela of encephalitis lethargica and occurs at high altitudes and in other severe anoxæmic conditions. The cH will be diminished (pH increased) and the total carbon dioxide diminished.

Table III summarises the findings in these four groups.

It will be seen that a non-gaseous acidosis and a gaseous alkalosis are both associated with a low total carbon dioxide content and likewise a low alkaline reserve. Similarly a gaseous acidosis and a non-gaseous alkalosis produce a high total carbon dioxide and a high alkaline reserve. This serves to illustrate the fallacy of using the alkaline reserve or the total carbon dioxide figure alone as an indication of the state of the acid-base balance.
CHAPTER IV

THE CARBON DIOXIDE DISSOCIATION CURVE

In the elucidation of the behaviour of the carbon dioxide and its method of transport in blood, one is concerned with two factors which are interdependent, namely, volume indicating the amount of the gas held in solution, and tension or pressure exerted by this gas. The explanation of these terms must be considered both in connection with a solution of carbon dioxide in a mixture of gases such as air and in a complex solution like blood.

**Tension or Partial Pressure of Carbon Dioxide in Air.**—In any given sample of air, as, for instance, alveolar air, the percentage of carbon dioxide can be readily estimated by means of a gas-analysis apparatus. Knowing this, one can ascertain what proportion of the atmospheric pressure (barometric pressure) in the gaseous mixture under consideration will be exerted by the carbon dioxide. A deduction, depending on temperature, must always be made for water-vapour, as it exerts pressure. At 37° C. this deduction is 47 mm. Hg. The calculation is as follows:

\[ Tension = \frac{\text{Percentage CO}_2 \times (\text{Bar. pressure} - \text{water-vapour})}{100} \]

If the percentage of carbon dioxide obtained on analysis be 5.5 volumes per cent. (as in normal alveolar air) and the barometric pressure 760 mm. Hg.

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the tension of carbon dioxide will be 39·2 mm. Hg. \( \frac{5.5 \times (760 - 47)}{100} \).

Conversely with a knowledge of the carbon dioxide tension, it is easy to calculate the volumes per cent. of the gas. Thus:

\[
\text{Percentage CO}_2 = \frac{\text{Tension of CO}_2 \times 100}{\text{Bar. pressure} - \text{water-vapour}}.
\]

**Tension of Carbon Dioxide in Blood.**—When dealing with carbon dioxide in solutions such as water or blood, the change from percentage to tension and *vice versa* is made in the same way as described above, except that in solutions the pressure of water-vapour obviously does not need to be taken into account and the coefficient of solubility of carbon dioxide in the solution concerned enters into the calculation. The coefficient of solubility for carbon dioxide in whole blood is 0.511. That is to say, 1 c.c. of blood at N.T.P. \((0\,\text{o C. and 760 mm. Hg.})\) will hold 0.511 c.c. carbon dioxide in simple solution.

The percentage of carbon dioxide in simple solution in blood cannot be determined by a single analysis as in air or in a fluid like water since twenty times as much carbon dioxide is carried in a combined form \((\text{NaHCO}_3)\) as is carried free. The method of determining the percentage of free carbon dioxide in blood is considered later.

If one does know the percentage of carbon dioxide in solution, *i.e.* the free carbon dioxide, its tension can be obtained as follows:

\[
\text{Tension} = \frac{\text{Percentage } \text{CO}_2 \times \text{Bar. pressure}}{100} \div 0.511
\]
or, conversely

\[ \text{Percentage } \text{CO}_2 \times 0.511 = \frac{\text{Tension CO}_2 \times 100}{\text{Bar. pressure}} \]

**THE NORMAL CARBON DIOXIDE DISSOCIATION CURVE**

If a sample of blood be exposed to an atmosphere containing a known tension of carbon dioxide for a period long enough to ensure equilibration, the tension of carbon dioxide in the blood will be the same as that of the atmosphere to which it was exposed. The total carbon dioxide content will also be altered relatively with this tension, but not proportionately because of the carbon dioxide carried in chemical combination as bicarbonate.

To obtain the necessary information to construct the carbon dioxide dissociation curve, blood is exposed to atmospheres containing carbon dioxide at different tensions. After time has been allowed for equilibration, the carbon dioxide contents of samples of the atmosphere and the blood are estimated, due precautions being taken of course, to prevent any loss of gas during the process. The results so obtained are plotted as in the diagram (Figure V).

This curve is known as the carbon dioxide dissociation curve or carbon dioxide absorption curve, and shows the power of the blood to take up carbon dioxide from atmospheres containing carbon dioxide at various pressures. Its consideration is of great value in an appreciation of the question of acid-base balance and its disturbances. The curve under normal conditions is constant for the individual and varies but little for different individuals. At a tension of carbon
dioxide of 40 mm. Hg. there are approximately 52 volumes per cent. of carbon dioxide present in fully oxygenated whole blood. In normal children the limits of variation at 40 mm. Hg. tension were found to be 47 to 56 volumes per cent. (Figure V). Peters, Barr, and Rule report the limits of normal for the same tension in adults to be 43 to 56 volumes per cent. In children, in whom acid-base balance disturbances occur more frequently than in adults, one might have expected wider variations of the normal limits.

FIGURE V
SHOWING THE VOLUMES PER CENT. OF CARBON DIOXIDE AT VARIOUS TENSIONS (DATA OBTAINED FROM THE BLOOD OF TEN NORMAL CHILDREN). THE AVERAGE NORMAL AND THE LIMITS OF NORMAL ARE SHOWN.
ACIDOSIS AND ALKALOSIS

It is still under discussion whether the dissociation curve determined from fully oxygenated venous blood gives a correct picture of the condition of arterial blood. Acid substances are produced in the tissues, especially during work, and the presence of these lowers the carbon dioxide combining capacity of the blood. These acid substances, however, are not given off in the lungs, but are carried over into the arterial system, and in that respect there is no difference between arterial and venous blood. Investigators differ as to the similarity of carbon dioxide dissociation curves of fully oxygenated arterial and venous bloods. Some believe that there is little difference while others maintain that marked differences exist. It must be admitted that, in disease, where there may be pathological conditions such as a marked relative increase in the corpuscular volume of venous blood, the carbon dioxide curves in venous and arterial bloods may show considerable differences.

ABNORMAL CARBON DIOXIDE DISSOCIATION CURVE

In conditions in which the acid-base balance is disturbed, the carbon dioxide dissociation curve departs from normal. Two abnormal types may be found: (1) hypocapnic, in which the curve is shifted to the right, that is, at any given tension, the total content of carbon dioxide is lower than normal; and (2) hypercapnic, in which it is shifted to the left, that is, at any given tension, the total content of carbon dioxide is greater than normal. The direction of deviation of the curve from the normal does not determine whether there is a state of alkalosis or
acidosis. If, however, in addition to the dissociation curve, the total carbon dioxide content of the arterial

FIGURE VI
SHOWING THE NORMAL AND THE TWO TYPES OF ABNORMAL CARBON DIOXIDE DISSOCIATION CURVES.

blood be known, it is possible to determine the figures for both the free and combined carbon dioxide and
ACIDOSIS AND ALKALOSIS

hence the pH of that sample of blood can readily be ascertained (see arterial point on carbon dioxide dissociation curve, Chapter VI, page 54).

_Hypocapnic Curve._—Curve A (Figure VI) was obtained from the blood of a child suffering from salicylate poisoning. The curve is shifted to the right. This might be due either to the over-production of acid substances such as occurs in diabetic coma, with consequent diminution in the available alkali (non-gaseous acidosis), or to the over-stimulation of the respiratory centre with "washing-out" of the carbon dioxide by over-ventilation (gaseous alkalosis). The total carbon dioxide content of the blood was 32.4 volumes per cent.; by using this figure to mark the arterial point on the carbon dioxide dissociation curve (Chapter VI) and applying Hasselbalch's equation, we find that the pH is 7.28, which is to the acid side of normality. The condition present was therefore a non-gaseous acidosis.

_Hypercapnic Curve._—Curve B (Figure VI) was obtained from the blood of an infant with congenital pyloric stenosis. It is shifted to the left. This might be due either to a diminution of the acid radicles (non-gaseous alkalosis) or to depression of the respiratory centre with decreased output of carbon dioxide (gaseous acidosis). The volume of breathing would be diminished in both conditions. In this particular case the respiratory rate was 10 per minute. The total carbon dioxide content was 110 volumes per cent. and the pH calculated as in the previous instance was 7.63, indicating a marked degree of alkalinity. The condition present in this infant, therefore, was a non-gaseous alkalosis.
THEORETICAL CURVES.

It has been shown by Barcroft, Dryerre, Meakins, Parsons and Parsons that, given the carbon dioxide content of the blood at two tensions and the pH of the blood at one of them, an accurate carbon dioxide dissociation curve can be constructed. We have constructed several such “theoretical” curves, and found them to agree with the one determined in the usual way. That a curve of this nature can be constructed from such data is good evidence of the exactness of the physiological regulation of the acid-base balance of the blood.
DEFENCES AGAINST ACIDOSIS

In the course of normal metabolism acid products are being constantly produced in excess of base. It is necessary, therefore, that there should be some mechanism for dealing with this excess formation of acid products of metabolism. Furthermore, the provision for the disposal of acid must be greater than the arrangements for combating an excess of base. The latter eventuality can be readily corrected by cutting down the excretion, and increasing the production of some of the normal acid metabolites, using the products of normal metabolism (carbonic, lactic, and phosphoric acids) to neutralise the excess alkali. Excess acid cannot be similarly dealt with by a utilisation of base since practically none of the products of metabolism is alkaline in nature. Accordingly, a breakdown of the defences against acidosis should be more serious than the collapse of those against alkalosis. Such is, in fact, the case. An attack of acidosis is very frequently an acute condition which may and often does cause the rapid death of the patient. Alkalosis, on the other hand, seldom endangers life.

The defences against acidosis comprise buffer action
in the blood and tissues, and the excretory functions of the lungs and kidneys. The whole mechanism is so delicately adjusted and the various processes are so interdependent that it is necessary to take account of all the defensive reactions whenever an instance of disturbance of acid-base equilibrium comes under consideration. An understanding of the principles underlying these reactions helps materially in the recognition of many clinical states.

**BUFFER ACTIONS IN THE BLOOD**

**Carbonic Acid-Bicarbonate.**—Of the acids produced in the course of metabolism, phosphoric, sulphuric, lactic, and the other organic ones are neutralised immediately after formation, so that they are always present in the blood and tissue-fluids as salts. Carbonic acid, on the other hand, is not completely neutralised and indeed, is found in the blood in quite appreciable amounts as a free acid in solution. In this connection two important facts about carbonic acid must be remembered: (1) with sodium bicarbonate it forms an important buffer, (2) it is the ratio of free carbonic acid to bicarbonate which regulates the activity of the respiratory centre. Any change which results in the amount of free carbon dioxide becoming relatively greater than that of the combined carbon dioxide will stimulate the centre to greater activity and, vice versa, any factor which reduces the ratio will depress respiratory activity. Thus, carbonic acid must be regarded not as a mere waste product but as an important part of the system present in the blood and tissues for regulating their reaction.

If the blood is called upon to dispose of some excess
acid (HA) the bicarbonate immediately "soaks up" the acid according to the equation,

$$\text{BHC}O_3 + \text{HA} \rightleftharpoons \text{BA} + \text{H}_2\text{CO}_3.$$  

It is clear that some of the combined carbon dioxide is used up and therefore diminished in amount while the free carbon dioxide is increased and the ratio is increased. The respiratory centre is stimulated to greater activity, with the result that extra carbon dioxide is given off through the lungs. This continues as long as the ratio \(\frac{\text{H}_2\text{CO}_3}{\text{BHC}O_3}\) is above normal, i.e. until all the HA has been dealt with. This combination of buffer action with increased respiratory activity forms the first line of defence, and is in constant use dealing with the normal excess of acid over base production.

**Phosphates.**—Inorganic phosphates are present in two forms in the blood, as the alkaline salt (Na$_2$HPO$_4$) and as the acid salt (NaH$_2$PO$_4$). At the normal reaction of the blood there is four times as much of the alkaline as of the acid phosphate. These two salts are powerful buffers, but are present only in comparatively small amounts. They act similarly to bicarbonate.

$$\text{HA} + \text{Na}_2\text{HPO}_4 \rightleftharpoons \text{NaH}_2\text{PO}_4 + \text{NaA}.$$  

The advantage of this reaction is twofold, first, the dissociation, and therefore the acidity of the NaH$_2$PO$_4$ is less than that of the HA and, second, phosphates can easily and rapidly be excreted by the kidney.

**Proteins.**—The addition of acid to the blood also causes an immediate decrease in the acid value of the proteins, and consequently the liberation of a certain amount of base previously held by these proteins.

$$\text{HA} + \text{BPr} \rightleftharpoons \text{BA} + \text{HPr}.$$
As in the case of bicarbonates and phosphates the acidity of HPr is much less than that of HA.

**Hæmoglobin.**—Hæmoglobin acts as a weak acid at the reaction of the blood. That this is so is shown by a consideration of the changes in the carbon dioxide content of the blood when the pressure of carbon dioxide is reduced. A solution of NaHCO₃ when exposed to a Torricellian vacuum will give off only one-half of its carbon dioxide according to the equation

\[ 2\text{NaHCO}_3 \rightarrow \text{Na}_2\text{CO}_3 + \text{CO}_2 + \text{H}_2\text{O}. \]

The addition of a small amount of acid is required before the remainder is given off. Whole blood, when exposed to a vacuum, will part with practically all its carbon dioxide, provided it is shaken and sufficient time allowed. The small amount not expelled is that which remains free in solution by virtue of the solubility of carbon dioxide at the tension to which the blood is exposed. Furthermore, if a moderate amount of Na₂CO₃ be added to the blood, the carbon dioxide of the carbonate will also be given off. Blood-plasma, however, behaves like the aqueous solution of bicarbonate, and does not give off all its carbon dioxide unless an acid be added. There is clearly something in the corpuscles which acts as a weak acid. This substance is now recognised to be the hæmoglobin.

In virtue of its behaviour as a weak acid hæmoglobin is a buffer, and because of its amount, it is one of the most important buffers in the blood. Like the other proteins the degree of dissociation, and therefore its acidity, become less as the acidity of the containing fluid (plasma) becomes greater. If there is an excessive output of acid from the tissues the following reactions take place in the corpuscles:
ACIDOSIS AND ALKALOSIS

\[
\begin{align*}
HA + KHCO_3 & \rightarrow KA + H_2CO_3 \quad (1) \\
H_2CO_3 + KHb & \rightarrow KHCO_3 + HHB \quad (2).
\end{align*}
\]

In the first place the excess acid is dealt with by the potassium bicarbonate of the corpuscles. (There is no sodium in the red cells.) This leads to the formation of $H_2CO_3$ (equation (1)). The carbonic acid in turn reacts with the $Hb$ and produces more bicarbonate (equation (2)). The acidity of $HHb$ (hydrogen haemoglobin) is less than that of $H_2CO_3$. In addition, the $KHCO_3$ formed in equation (2) is ready to react with more $HA$ so that the reaction continues until all the $HA$ is neutralised or the supply of $Hb$ is finished. Once the normal reaction is again reached, say by an increased respiratory output of carbon dioxide, the equation (2) will take place in the reverse direction until the haemoglobin regains its full quota of base

\[
HHb + KHCO_3 \rightarrow KHb + H_2CO_3.
\]

The $H_2CO_3$ is split into $H_2O$ and $CO_2$ and the $CO_2$ is expelled.

If acid be added to blood during its passage through the tissues there will be associated with the above changes a removal of oxygen and a consequent reduction of a considerable amount of oxyhaemoglobin to reduced haemoglobin. This latter substance is much the weaker acid (it is sixty-seven times less dissociated than oxyhaemoglobin) so that because of this change, alkali is liberated for the neutralisation of acid. It has been calculated that four-fifths of the carbon dioxide given off by the tissues during the resting state is combined with alkali which has been liberated by the decreased acidity of haemoglobin due to its change from the oxy- to the reduced form. This accommodation of extra carbon dioxide by the change of oxy- to reduced
hæmoglobin has been called the *isohydric* transport of acid since it occurs without change in the hydrogen-ion concentration.

**Chloride Shift (Hamburger Phenomenon).—**If a sample of blood be exposed to an atmosphere rich in carbon dioxide the plasma will tend to become less alkaline than the corpuscles. In order to maintain the normal equilibrium between cells and plasma, the cells must either acquire more acid or get rid of some of their alkali. The cell-walls allow acid to pass through although they are impermeable to base. Thus, there ensues a passage of chlorine (Cl) and carbonic acid (H$_2$CO$_3$) from plasma to cells. The first of these events may be represented by the following equations:

1. in plasma, \[ H_2CO_3 + NaCl \rightarrow NaHCO_3 + HCl. \]
2. in corpuscles, \[ HCl + KHb \rightarrow HHb + KCl. \]

It will be seen that by the transference of chlorine from plasma to red cells the amount of base in the plasma left for combination with carbonic acid is increased. Thus the reaction of the plasma is approximated to that of the red cell. The greater the degree of acidosis, the greater is the migration of chlorine to the corpuscles.

It is now apparent that the amount of carbon dioxide taken up by a given sample of blood is very largely dependent on the hæmoglobin content. The more hæmoglobin present, the more chlorine will be able to migrate into the red cell, since this chlorine is accommodated in the corpuscles by the liberation of base previously combined with the hæmoglobin. As has already been pointed out, the reduction of oxyhæmoglobin plays an important part here, reduced hæmoglobin being less acid than oxyhæmoglobin.
Apart from the accommodation of the migratory chlorine ions, the red cells are also permeable to carbon dioxide, so that carbonic acid may be fixed by corpuscular base (potassium) which has been released from hæmoglobin and alkaline phosphate.

$$\text{KHb} + \text{H}_2\text{CO}_3 \rightarrow \text{HHb} + \text{KHCO}_3$$

$$\text{K}_2\text{HPO}_4 + \text{H}_2\text{CO}_3 \rightarrow \text{KH}_2\text{PO}_4 + \text{KHCO}_3.$$  

The buffering mechanism in the blood is due, therefore, to the presence of bicarbonate, phosphate, and proteins, the chief of which is hæmoglobin. It can accordingly be readily appreciated that disturbances of acid-base balance occur more readily and are more serious whenever the hæmoglobin is deficient (anæmia).

The efficiency of any buffer system in resisting change in reaction is at its maximum when the contents of salt and acid (e.g. sodium bicarbonate and carbonic acid) are equal. The following table shows the pH values at which the buffering systems contain equal amounts of the two factors and therefore at which the buffers are most efficient:

<table>
<thead>
<tr>
<th>Buffer System</th>
<th>pH Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{CO}_3$</td>
<td>$\text{BHCO}_3$</td>
</tr>
<tr>
<td>$\text{BH}_2\text{PO}_4$</td>
<td>$\text{B}_2\text{HPO}_4$</td>
</tr>
<tr>
<td>$\text{HHbO}_2$</td>
<td>$\text{BHbO}_2$</td>
</tr>
<tr>
<td>$\text{HHb}$</td>
<td>$\text{BHb}$</td>
</tr>
</tbody>
</table>

It is apparent that the pH of maximum efficiency of each system except hæmoglobin lies below the normal range for blood. Accordingly these buffer systems will act in the blood with increasing efficiency as the pH falls—more evidence that the body is better protected against acidosis than alkalosis.

In close association with, and indeed, essential to this line of defence against acidosis is a healthy respiratory system since the buffering processes result
AGAINST ACIDOSIS AND ALKALOSIS

in a relative increase of free carbon dioxide and, therefore, a fall in pH. This fall is counteracted by the increased respiratory activity, which leads to a reduction in the free carbon dioxide and a return to normal pH.

THE RÔLE OF THE KIDNEY

The buffer system of the blood even with the help of the respiration would be frequently overwhelmed if the defence against acid accumulation ended there. Just as hæmato-respiratory processes are the chief agents for dealing with carbon dioxide, the kidney is undoubtedly the principal path for the excretion of all other acid radicles. The sweat glands may play an important part in the metabolism of chlorine when large amounts of sweat are produced, although it has been estimated that not more than one gramme of sodium chloride is excreted daily even during profuse perspiration.

Urinary Acidity.—The urinary pH cannot sink much below 4·5, and at this reaction none of the stronger acids can be excreted unless they are neutralised by alkali. The weaker acids, however, have pH values within the urinary range, and thus can be excreted free and unaccompanied by base. This has the double advantage, first, of getting rid of acid and, second, of freeing the alkali with which these weak acids have been united in the blood, thus permitting the use of the alkali so liberated for the neutralisation of stronger acids. The alkali saved by the excretion of un-neutralised weak acids amounts, however, to but a small fraction of the total quantity required. It certainly would be inadequate to meet requirements in even the mildest degree of acidosis.
Ammonia Excretion.—In intermediate metabolism the amino-group \((\text{NH}_2)\) is converted into ammonia, which is available for neutralisation of acids to form salts. Under normal conditions the bulk of the ammonia fastens on to carbon dioxide to become ammonium carbonate from which, by the loss of two molecules of water, the innocuous substance urea is formed. This is accomplished by the liver:

\[
2\text{NH}_2 + \text{CO}_2 \rightleftharpoons \text{NH}_4\text{COONH}_4 \rightleftharpoons \text{NH}_4\text{COONH}_4 \rightleftharpoons \text{NH}_2
\]

It has been clearly demonstrated by Benedict and Nash that a re-synthesis of ammonia takes place in the kidney. The amount of ammonia formed in the kidney seems to depend upon the quantity of strong acid requiring to be excreted. In health 90 per cent. of the total urinary nitrogen is excreted as urea and 3–5 per cent. as ammonia. Under the stress of acidotic conditions 20 per cent. or more of the nitrogen may appear as ammonia, indicating the amount of excess acid to be neutralised. The information obtained from the determination of the amount of ammonia relative to total nitrogen excreted is expressed as the ammonia coefficient,

\[
\frac{\text{Ammonia Nitrogen}}{\text{Total Nitrogen}} \times 100.
\]

Supply of Fixed Base.—The increase in ammonia excretion takes some days to reach its maximum (Figure VII), so that some other arrangement is necessary to tide over the delay. This is provided by a supply of extra base directly from the bones as
AGAINST ACIDOSIS AND ALKALOSIS

calcium, and from the soft tissues as sodium and potassium. In contrast to the ammonia output the increased excretion of fixed base takes place immediately (Figure VII).

**FIGURE VII**

*SHOWING DAILY URINARY OUTPUT OF AMMONIA, FIXED BASE AND TITRATABLE ACID BEFORE AND DURING ACIDOSIS PRODUCED BY AMMONIUM CHLORIDE.*

(From Morris and MacRae, *Arch. Dis. Child.*, 1930, v, 218.)

The calcium is present in bone as calcium carbonate (CaCO$_3$), one-fifth, and calcium triphosphate (Ca$_3$(PO$_4$)$_2$), four-fifths. The carbon dioxide of the calcium carbonate is readily excreted by the lungs, but the phosphorus, an acid radicle, must be got rid
of by the kidney or bowel. By the excretion of phosphorus in the urine however, there is a valuable saving of base since phosphorus neutralises three equivalents of monovalent base in bone, but only one in the urine. This results in a saving of two equivalents of base for each equivalent of bone phosphorus excreted by the urine. For the faeces the saving is somewhat less.

In their excretion the sodium and potassium of the tissues bring with them water to prevent disturbances of osmotic equilibrium which would otherwise occur. This is the explanation of the diuresis which occurs at the commencement of an acidosis, and when ammonia formation is not great enough, as in interstitial nephritis, to cope with all the acid requiring excretion. This loss of base and water is one of the serious and harmful effects of an acidosis of any severity and duration.

In the post-acidotic state the loss of tissue base is made good by the continued formation in the kidney of ammonia in excess. Thus, base derived from the diet is allowed to accumulate in the bones and soft tissues until the previous loss is made good.

**FORMATION OF ORGANIC ACIDS**

It has recently been shown that organic acids play an important part in the excretion of excess acid or alkali. In acidic conditions except those due to ketone production there is a decrease of organic acids in the urine, which is due either to lessened production or to better combustion. In alkalosis, on the other hand, organic acids are formed and excreted in larger amounts. The excess alkali is thus neutralised and its excretion within the limits of
the hydrogen-ion concentration of the urine is made possible.

RÔLE OF THE INTESTINE

There is no doubt that the intestine plays an important part in the excretion of minerals, especially calcium and phosphorus. It is extremely doubtful, however, if it exerts any other protective action in the prevention of acidosis and alkalosis. In pathological conditions such as excessive diarrhoea or vomiting, the acid-base equilibrium may be profoundly affected, but no definite evidence is available of any defensive mechanism associated with the bowel.

DEFENCES AGAINST ALKALOSIS

As we have already stated, owing to the ease with which the body can accumulate acid, alkalosis is not of such urgent moment to the individual as is acidosis. Nevertheless, a mechanism exists to prevent the reactions of the blood and tissues from becoming too alkaline. In order to achieve this object and counteract an alkalosis, the following reactions are available.

Haemato-respiratory.—In non-gaseous alkalosis excess of base is compensated for by the retention of carbon dioxide: this is affected by depression of respiration. In gaseous alkalosis, on the other hand, excess of base cannot be so rectified, for it is pulmonary over-ventilation itself and consequent excess excretion of carbon dioxide which determines the condition. Buffer and renal action have to be utilised in such instances.

Buffer Action.—This is similar to what occurs in acidosis except that the reactions take place in the opposite direction. For example, proteins become
more acid, and are thus able to hold more base, and chlorides shift from corpuscles to plasma.

Renal.—The urine becomes more alkaline due to the excretion of greater amounts of alkaline phosphate (\( \text{Na}_2\text{HPO}_4 \)) and carbonate. Simultaneously there occurs a decreased formation of ammonia which necessitates a rise in the excretion of fixed alkali in combination with acid, and the call upon base is further increased by the additional formation of organic acid.

Another important acid-sparing substance is carbonic acid. This unites with the base requiring excretion in the urine, and thus does away with the necessity of utilising some other acid-radicle such as chlorine or phosphorus. Once the pH of the urine exceeds 6.4, carbonic acid appears in steadily increasing amounts, and conserves the fixed acid.

**PHYSIOLOGICAL VARIATIONS OF ACID-BASE EQUILIBRIUM**

Effect of Food.—About one hour after breakfast there is a rise in the bicarbonate of the blood, which is the result of the loss of chlorine secreted in the gastric juice. Simultaneously the urine becomes more alkaline. This phenomenon is known as the "alkaline tide," and is most marked in patients with hyperchlorhydria and absent in those with achlorhydria. When the food has passed into the intestine and reabsorption of the chlorine of the gastric juice is taking place, the bicarbonate and chlorine of the blood gradually regain their normal levels, and the urinary reaction returns to its usual acidity. The alkaline tide is not so marked, and may even be absent
after meals taken later in the day, since it is masked by the effects of the previous meals and the acids produced by muscular exercise.

In health, carbohydrate and fat are completely oxidised to carbon dioxide and water, which are removed so quickly that no disturbance of acid-base equilibrium is apparent. The oxidation of protein leads to the formation of sulphates and phosphates, so that a high protein diet has an "acid" effect. The amount of minerals, whether acid or alkaline in nature, influences acid-base equilibrium in the corresponding direction, but the excretory system is usually capable of preventing any manifest changes.

Inanition by the production of acid metabolites leads to a lowering of bicarbonate and the appearance of large amounts of acid and ammonia in the urine. In some children a severe inanition acidosis may develop fairly rapidly.

Muscular Exercise.—Muscular contraction leads to the production of lactic acid, some of which is re-synthesised to glucose, and some oxidised to carbon dioxide. When this takes place immediately, no obvious effect is noted on acid-base equilibrium, since a slight increase in pulmonary ventilation is sufficient to remove the extra carbon dioxide. If, however, the muscular exercise is of such a nature that sufficient oxygen cannot be taken in to complete the oxidation of lactic acid immediately (oxygen debt), this substance appears in excess in the blood. Accordingly the bicarbonate of the blood is reduced, and the pulmonary ventilation increased and, if this does not suffice to maintain the ratio of free carbon dioxide to combined carbon dioxide at 1 : 20, there is a fall in the pH. The urine shows an increase in acidity and ammonia.
ACIDOSIS AND ALKALOSIS

**Heat.**—The application of heat (e.g. immersion in a hot bath), leads to excessive pulmonary ventilation with consequent washing out of free carbon dioxide and the production of a gaseous alkalosis.

**Exposure to Low Oxygen Pressure at High Altitude.**—This also leads to rapid shallow breathing with washing out of carbon dioxide and the production of a gaseous alkalosis. The urine is alkaline. Sickness and vomiting often occur (mountain sickness).

**PATHOLOGICAL VARIATIONS IN ACID-BASE EQUILIBRIUM**

All pathological changes in acid-base balance are the result of an impaired function or an over-taxing of one or more of the protective mechanisms. Details connected with various diseases associated with acidosis or alkalosis are discussed later. Meanwhile, it is of advantage to summarise the various processes which may lead to disturbances of acid-base equilibrium. They must be due to excess or deficiency of either acid or base and the following scheme adapted from Marriott shows how these factors may act.

**ACIDOSIS**

Tendency toward, or actual reduction of $\frac{H_2CO_3}{BHCO_3}$ ratio.

1) *Non-gaseous.*—Where pathological factor affects the denominator primarily.

(a) Reduction of $BHCO_3$ due to neutralisation of acids due to

(i) Increased formation of acid, *e.g.* ketone bodies in diabetic acidosis: lactic acid in muscular exercise.
AGAINST ACIDOSIS AND ALKALOSIS

(ii) Administration of acid-producing substances, *e.g.* HCl, NH₄Cl, CaCl₂: high fat diet (ketogenic diet) leading to production of ketone bodies.

(iii) Impaired urinary excretion of acid, *e.g.* phosphates in interstitial nephritis.

(b) Loss of fixed base—excessive excretion.
   (i) By intestinal tract—diarrhoea.
   (ii) By urine—when ammonia formation is impaired in kidney.

(2) *Gaseous.*—Where pathological factor affects the numerator (\(H₂CO₃\)) primarily.
   (a) Increase of \(H₂CO₃\).
      (i) Depression of respiratory centre.
      (ii) Impairment of circulation.
      (iii) Pulmonary impairment.

ALKALOSIS

Tendency toward, or actual rise of \(\frac{H₂CO₃}{BICO₃}\) ratio.

(1) *Non-gaseous.*—Where pathological factors affect the denominator primarily.
   (a) Increase of bicarbonate.
      (i) Administration of alkali in certain cases.
      (ii) Deficit of acid and its replacement by \(H₂CO₃\).
         (1) Loss of chlorine by vomiting.
         (2) Oxidation of ketone acids after insulin in diabetes.

(2) *Gaseous.*—Where pathological factors affect the numerator (\(H₂CO₃\)) primarily.
   (a) Decrease in \(H₂CO₃\).
      (i) Hyperventilation.
CHAPTER VI

THE DETERMINATION OF THE STATE OF THE ACID-BASE EQUILIBRIUM

THE DETERMINATION OF THE pH

The reaction of the blood (pH) may be arrived at in two ways: (1) directly, by an electrometric or a colorimetric method, and (2) indirectly, by the estimation of the free and combined carbon dioxide and the use of Hasselbalch’s equation.

Direct Determination.—The electrometric method involving the use of the hydrogen or glass electrode is the standard by which the others are judged. The principles underlying the use of this method are given in text-books of biophysics. The normal range of the pH of arterial blood estimated by such a method is generally taken to be 7·80 to 7·50.

In the colorimetric methods a dialysate or a diluted sample of the blood is obtained without loss of carbon dioxide and an indicator with a colour change covering the blood pH range 6·8–8·0 is added. The colour so produced is matched with one of a series of standard solutions of known pH. “The result obtained by the colorimetric methods (at 20° C.) for blood equilibrated at 38° C. is higher by about pH 0·2 than that obtained by the electrometric method at 38° C. This effect is, due partly to the difference of temperature and partly to dilution, but chiefly to the former” (Lovatt Evans).
**Indirect Methods.**—These are all dependent on the determination of the value of the ratio $\frac{\text{free } \text{CO}_2}{\text{combined } \text{CO}_2}$. The total carbon dioxide content is readily obtained by means of a blood-gas analysis apparatus. In order to complete the information required, it is necessary to ascertain either the free or the combined carbon dioxide separately. Usually, the free carbon dioxide is determined, the value for the combined carbon dioxide being obtained by subtracting the free from the total carbon dioxide.

The value for free carbon dioxide may be obtained in one of the following ways: (1) by analysis of a sample of alveolar air, or (2) by the determination of the arterial point on a carbon dioxide dissociation curve.

**Alveolar Air.**—The volume of a gas that is held in solution by a fluid varies directly with the pressure of the gas to which the fluid is exposed. Hence, it is usually stated that the tension of carbon dioxide in arterial blood is the same as that in the alveolar air. As a rule this holds good, but in certain conditions, particularly those associated with cardiac dyspnœa and primary lung disease, differences may occur between the tensions of carbon dioxide in alveolar air and arterial blood due to impairment of gaseous interchange.

If samples of alveolar air are obtained and analysed, the determination of the amount of free carbon dioxide becomes a simple arithmetical calculation. Thus, Percentage of CO$_2$ in alveolar air $= 5.5$

Tension of CO$_2$ in alveolar air $= \frac{5.5 \times (760 - 47)}{100}$

$= 39.2 \text{ mm. Hg.}$
Free CO₂ in the blood $= \frac{39.2 \times 100 \times 0.51}{760}$
$= 2.79$ volumes per cent.

Total CO₂ (determined by Hal-dane's apparatus on a sample of blood) $= 62.7$ volumes per cent.

Therefore, combined CO₂ in the blood $= 59.91$ volumes per cent.

$$\text{pH} = pK_1 + \log \frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3}$$
$$= 6.10 + \log \frac{59.91}{2.79}$$
$$= 7.43.$$

In adults it is possible, although not easy in an untrained subject, to obtain accurate samples of alveolar air. In children, however, the variations found in the compositions of successive samples of supposed alveolar air are in our experience so great that the procedure is useless.

**Arterial Point on Carbon Dioxide Dissociation Curve.**—The arterial point is that point on the carbon dioxide dissociation curve of the blood of the patient which corresponds to the value for the total carbon dioxide content of the arterial blood of the patient. Arterial blood is obtained from the radial artery at the wrist or femoral artery in the groin: its total carbon dioxide content is determined, and it is then exposed to varying tensions of carbon dioxide gas and a carbon dioxide dissociation curve is constructed. For example,
the arterial carbon dioxide content in a patient (T. C.) was found to be 45 volumes per cent. The carbon dioxide dissociation curve with the arterial point \( (\times) \) is shown in Figure VIII. From the curve it is clear that a carbon dioxide content of 45 volumes per cent. corresponds to a tension of 40 mm. of mercury. By means of Bohr's coefficient of solubility for carbon dioxide in whole blood (0.51) it can be readily calculated that this tension corresponds to

\[
\frac{40 \times 100 \times 0.51}{760}
\]

\( i.e. \) 2.68 volumes per cent. of carbon dioxide in solution or free carbon dioxide. The combined carbon dioxide must therefore be 45 - 2.68, \( i.e. \) 42.32. Accordingly,
Single Examinations of the Blood.—In practice, blood examinations have generally to be done on venous blood. Arterial blood in infants and young children cannot be obtained except in rare instances: at least we have not been successful with arterial puncture. The analysis of venous blood, however, yields results of considerable practical value.

The total carbon-dioxide content of the whole blood is decreased in conditions of non-gaseous acidosis and gaseous alkalosis, and increased in gaseous acidosis and non-gaseous alkalosis. Hence it may be misleading to use determinations of the total carbon dioxide alone as conclusive evidence of the state of the acid-base balance. This value in conjunction with the clinical signs, however, is usually sufficient. The common acidotic conditions belong to the non-gaseous group, and in diseases in which this type of disturbance is prone to occur, e.g. diabetes and gastro-enteritis, a low carbon dioxide content may be taken as satisfactory evidence of the presence of acidosis. Similarly, in an alkalosis such as occurs in pyloric stenosis, where the change is known to be of the non-gaseous type, the carbon dioxide content may be taken as an index of the degree of the alkalosis. The interpretation of any change in the total carbon dioxide content should be made only in conjunction with the clinical signs presented by the patient.

The alkaline reserve or the carbon dioxide combining power of the blood has a similar significance to that of the total carbon dioxide.

Certain observers lay stress on the figure for the
total carbon dioxide of the true plasma rather than that of the blood. Although the former is of more importance in a scientific study of acid-base equilibrium, it is more difficult to obtain accurately and is not of any greater value in clinical work. If the figure for the true plasma is required, it can be calculated from a graph which shows the relationship between the total carbon dioxide of the whole blood and that of true plasma (Medical Research Council Report, No. 72, "The Acid-Base Equilibrium of the Blood, 1923," page 24).

**URINARY TESTS**

**Acidity.**—Variations in the excretion of acid and alkali in the urine have for many years been made use of as an index of the conditions of the acid-base balance. The more acid excreted by the kidney, the lower is the pH of the urine and the greater its titratable acidity.

Leathes has described a method of double titration of the urine, using methyl orange and phenolphthalein as indicators. This shows the proportion of the alkaline to the acid phosphate in the urine. The greater the degree of acidosis, the more phosphate will be excreted as the acid salt ($\text{NaH}_2\text{PO}_4$). Accordingly the ratio $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4}$ in the urine provides an indication of the state of the acid-base equilibrium.

Sellards devised a method of estimating the degree of acidosis in the acid-poisoning type. The principle of this method lies in determining the amount of sodium bicarbonate given by mouth necessary to render the urine alkaline. Normally, the ingestion of
5 grammes is sufficient, but in a patient with well-marked acidosis, 30 grammes or more may be necessary. The more required, the more severe is the acidosis. If the administration of 5 grammes of sodium bicarbonate renders the urine alkaline it is justifiable to conclude that an acidosis is not present. But, on the other hand, if the urine still remains acid even after much more than 5 grammes, any conclusion drawn on the strength of this finding is liable to be wrong.

**Ammonia Coefficient.**—The appreciation of the fact that the ammonia output is increased in acidosis dates from the work of Walther in 1877. At that time he found that the administration of dilute hydrochloric acid to rabbits caused a marked increase in rate and depth of breathing. When he repeated these experiments on dogs with comparable doses of acid, the effect was either lacking or much less marked. On investigating the cause of this difference he found that there was a greatly increased output of ammonia in the urine of the dogs. In carnivores such as the dog and man, there is, probably because of the necessity of neutralising the acid catabolites of protein, an ammonia-forming mechanism which is much less developed in herbivorous animals such as rabbits. Walther estimated the degree of acidosis by the extent to which the ammonia output was increased. It is clear, however, that the ammonia output depends also on the amount of nitrogen requiring excretion. It is customary, therefore, to pay attention, not to the absolute amount of ammonia excreted but to the relationship of this to the total output of nitrogen. The term ammonia coefficient is used to represent the percentage of the total urinary nitrogen which is excreted as ammonia nitrogen. It will be remembered
that ammonia in the urine may take the place of, and by this means, spare fixed base: it is formed in increased amounts when there is a demand for base to neutralise excess acid. In these circumstances, since the total nitrogen excretion does not increase pari passu, the ammonia coefficient rises. Normally this varies from 3 to 5, but in a non-gaseous acidosis it may rise above 20.

Hasselbalch showed that the ammonia coefficient bore a relationship to the pH of the urine. At a urinary pH of 5.8 the ammonia coefficient varied in healthy individuals between 2.2 and 5.5, but was much more constant for the one person. The ammonia coefficient at pH 5.8 he has called the "reduced ammonia coefficient." It must be remembered, however, that the relationship between urinary pH and ammonia coefficient is always altered when a diet poor in protein is given.

Another modification of the ammonia coefficient is to determine the ratio of acid (free and combined with ammonia) to total nitrogen, i.e.

$$\frac{\text{Titratable acid} + \text{Ammonia}}{\text{Total nitrogen}}$$

This is probably of greater value than the simple ammonia coefficient.

Still another ratio, $\frac{\text{Titratable Acid}}{\text{Ammonia}}$, has been utilised. Normally this is below 1.0, but in nephritis ammonia excretion is impaired, and the ratio may rise to values greatly exceeding this figure.

The simplicity of most of these urinary tests is a point in their favour, but the great objection is that they all presuppose a normally functioning kidney, a
supposition which is not always justified even in patients without nephritis. Further, it is not infrequently the impaired kidney function itself which determines the presence of the acidosis, as in chronic interstitial nephritis.

**CLINICAL OBSERVATIONS**

The clinical signs and symptoms depend on the nature of the acidosis. In the gaseous type, which is rare, the breathing is slow, because the respiratory centre is depressed, and therefore requires more carbon dioxide to stimulate it. The patient is generally drowsy or comatose.

In the non-gaseous type there is often apparent the classical picture noted in diabetic acidosis. The most distinctive sign is the air-hunger of Kussmaul. Pulmonary ventilation in the severe case is greatly increased, but the increase in rate is not so marked as the increase in depth. The breathing is pauseless and noisy, being often readily heard on entering the sickroom. The recognition of this type of breathing is important, as it not infrequently happens that in young children it may be taken as evidence of pneumonia. In pneumonia, however, the frequency is increased, and the depth, if any change is appreciable, diminished. Cyanosis is not associated with the acidotic type of breathing unless there be cardiac involvement; this "acyanotic dyspnœa" is in contrast to the condition existing in pulmonary diseases. In acidosis the lips have been described as "cherry-red," but this observation is of little actual value except to call attention to the absence of cyanosis.
In the commoner type of alkalosis (non-gaseous) the breathing is depressed to conserve carbon dioxide in an attempt to restore the 1:20 ratio. In pyloric stenosis in infancy the respiratory rate may fall to six per minute, long apnæic periods are present, and the respirations are shallow. The infants have often the appearance of being drugged. In certain gastric conditions, especially in older children and adults treated by large doses of alkali, mental depression and changes in behaviour have been ascribed to the presence of alkalosis.

Gaseous alkalosis, on the other hand, is produced by rapid breathing, which "washes out" the carbon dioxide. This is seen experimentally in forced respirations and clinically, in mountain sickness, and as a sequela of encephalitis lethargica.

The multiplicity of the various tests devised from time to time for the recognition of acidosis and alkalosis is ample proof of the difficulty of finding any simple, and at the same time accurate method of determining the state of the acid-base equilibrium. Apart from the actual determination of the pH there is not, nor is there likely to be, a single test which can be considered infallible. Hence we would stress the necessity of taking into account the clinical history and findings as well as the laboratory tests in coming to any decision. Even the direct determination of the pH is often of very little use since well-marked clinical examples of acidosis may occur in which no change in the pH can be demonstrated. Furthermore, a single determination of the pH of the blood is of little value unless the limits of normal for the individual by the particular method used, are known. For instance, a pH of 7·30 in a subject whose normal pH is 7·40 would
represent a well-marked acidosis, while in another person a figure of 7.30 might be quite normal. Furthermore, the direct determination throws no light on the mechanism which has been brought into play to produce the disturbance in acid-base equilibrium. In other words, it cannot distinguish between a gaseous and a non-gaseous change. By the indirect method these facts are revealed and permit of a more accurate estimation of the nature of the change present. It is quite obvious, however, that neither method can ever become a routine clinical procedure. Nevertheless, in many diseases our knowledge of acid-base disturbance is so scanty that it would be of the greatest value if, in all conditions where acid-base disturbance is suspected to occur, a certain number of cases could be thoroughly worked out. This would obviate the fallacies entailed in hazarding an opinion from a single pH figure or from an isolated estimation of the alkaline reserve. A detailed knowledge of the changes occurring in any given condition would endow a figure for the alkaline reserve or ammonia coefficient with great value and permit of the longer and more difficult procedures being dispensed with.
CHAPTER VII

DIABETES

The acidosis occurring in diabetes mellitus is probably the best known disturbance of acid-base equilibrium, being, indeed, the classical example of non-gaseous acidosis. It depends for its production on the imperfect oxidation of fats leading to the over-production of ketone bodies (acetone, aceto-acetic acid, β-hydroxybutyric acid). Owing to the acid nature of these substances the bicarbonate content of the blood is lowered and all the other defensive reactions against acidosis are called into play. These have already been dealt with, but it may be permitted briefly to summarise them here. There is a reduction in both the chlorine and the carbon dioxide of the blood to make room for the excess of keto-acids. The free carbon dioxide is relatively less diminished than is the combined so that the pH tends to fall. Accordingly the pulmonary ventilation is increased so that the removal of free carbon dioxide is accelerated. The kidneys secrete a more acid urine and form more ammonia. There is also a call on the fixed base and fluid of the tissues for the neutralisation of acid: this facilitates the excretion of the excess acid, but necessitates the loss of a certain amount of tissue water. The copious excretion of urine with its high content of fixed base diminishes the total content of base in the body as a whole, although it is only late in the disease that there
is actually a reduced concentration of base in the blood. As long as these reactions are sufficient to cope with the excess of acid substances, the acidosis is only potential. Once, however, the acid bodies commence to accumulate in the blood and tissues, either because of massive over-production or of relative incapacity of the excretory mechanisms, a state of manifest acidosis is very quickly produced, and the pH of the blood may fall to a very low level.

**FAILURE OF DEFENSIVE REACTIONS**

The danger points in the defensive reactions are reached when lack of fluid prevents the proper utilisation of tissue-base and where the kidneys are unable to manufacture sufficient ammonia and excrete the acid products of metabolism. The figures in Table IV, which refer to the case of a diabetic patient before and during treatment with insulin, show the great extent to which the ammonia is called upon for the neutralisation of acid.

The patient was on exactly the same diet during the
two periods (five days each). In the second period, insulin was given so that carbohydrate metabolism was normal, and there was no excess of ketones in the urine. The excess ketone production necessitated the additional formation and excretion of 809 c.c. N/10 ammonia per day for neutralisation of the acid ketones, i.e. the ammonia production was more than trebled.

It can thus be easily understood how, when ammonia production reaches its maximum and can no longer cope with the excess ketones, an accumulation of acid may easily occur. It has been shown that the risks of coma in diabetes are very greatly increased when the patient is suffering from a chronic renal lesion such as interstitial nephritis, where ammonia production is defective.

As regards the supply of fluid it must be remembered that the presence of excess glucose in the blood acts as a diuretic. Consequently, there is a double demand on tissue-water: (1) to transport excess salts formed by combination of base with the excess acids, and (2) as a result of the diuretic action of glucose. This presumably explains the thin, dry appearance of many diabetics in the pre-insulin days. It also throws light on the danger of obesity in diabetes. Obesity is associated with relative impoverishment of extracellular water. Accordingly any demand for water will necessitate tissue catabolism in order to produce water, with the consequent formation of still more acid substances which in their turn demand still more alkali and water. Thus, a vicious circle is set up which can only be broken by preventing the formation of ketones. It should be recognised that the only real preventive of keto-acid production is an increased utilisation of carbohydrate.
ACIDOSIS AND DIABETIC COMA

The question arises as to the relationship between the acidosis and the condition of coma in diabetes. The dyspnœa can be accounted for entirely by the decreased alkalinity of blood and tissues. Actual coma, however, it is generally stated and accepted, must be the result of the presence of some factor other than simple acidosis. It has been suggested that any substance containing the "enol" grouping may produce coma. Acetone and kindred substances possess this chemical structure and it is quite possible that once the concentration of acetone bodies passes beyond a certain limit, coma is produced. Intravenous injection of acetone in amounts exceeding 1·5 grammes per kilogramme body weight in rabbits is followed by an immediate loss of consciousness. The concentration thus produced in rabbits' blood corresponds with the concentration of total acetone bodies found in the blood of comatose diabetics. In severe acidotic conditions other than those associated with excessive ketonæmia, coma is not a striking feature. Certainly, in pre-insulin days, the administration of alkali often led to the temporary disappearance of coma, but this finding is easily explained by the neutralisation and consequent excretion of keto-acids. Nowadays, injection of insulin, by enabling carbohydrate to be more efficiently utilised, accomplishes the same result much better, provided enough is given sufficiently early after the development of the coma. If, however, adequate treatment is not given early enough, coma continues and rapidly terminates in death. In one patient who was brought into hospital three days after the onset of coma, and who during that time had been
given only twenty units of insulin, it was possible by vigorous therapy to reduce the blood-sugar considerably and raise the blood-bicarbonate to a normal figure: nevertheless, the patient never regained consciousness. This seems to indicate that after a certain time irreparable damage of the tissue cells is produced so that re-establishment of normal acid-base equilibrium no longer suffices to produce recovery from coma.

TREATMENT OF DIABETIC ACIDOSIS

Although any full discussion of the treatment of diabetes is outwith the scope of this book, we must consider the treatment of the acidosis which, at any rate as far as children are concerned, is the chief cause of death. Of thirty cases of diabetes treated at the Royal Hospital for Sick Children, Glasgow, during the past nine years, thirteen died (twelve in their own
homes), and the cause of death in twelve of these was coma.

**Prophylaxis.**—The prevention of acidosis embraces almost the whole field of the treatment of diabetes mellitus. This is especially true of children, for in them intercurrent disease is not, as such, the cause of death. Joslin, writing of diabétés in childhood, says, "children in pre-insulin days lived in a state of coma deferred." For this reason we would emphasise the importance of continuous supervision in the treatment of the diabetic patient, especially the child (Table V). It is necessary in this connection to remember that the insulin requirements of a child are not stationary. Apart from the increase which becomes necessary as growth proceeds, the changes brought about by infection must not be forgotten (Table VI).

**Table VI**

**SHOWING INFLUENCE OF INFECTION ON THE INSULIN REQUIREMENTS OF THE DIABETIC.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Weight in Kg</th>
<th>Insulin Units</th>
<th>Blood-Sugar Fasting Mgm. %</th>
<th>Urine Sugar</th>
<th>Acetone</th>
<th>General Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.G.</td>
<td>26·1</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Well.</td>
</tr>
<tr>
<td></td>
<td>26·2</td>
<td>24</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Nasal catarrh.</td>
</tr>
<tr>
<td>W.D.</td>
<td>17·2</td>
<td>16</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>Well.</td>
</tr>
<tr>
<td></td>
<td>17·0</td>
<td>22</td>
<td>225</td>
<td>+</td>
<td>++</td>
<td>Septic wound of hand.</td>
</tr>
<tr>
<td>S.N.</td>
<td>21·5</td>
<td>20</td>
<td>81</td>
<td>-</td>
<td>-</td>
<td>Well.</td>
</tr>
<tr>
<td></td>
<td>21·2</td>
<td>44</td>
<td>124</td>
<td>++</td>
<td>-</td>
<td>Influenza.</td>
</tr>
</tbody>
</table>

Even an afebrile catarrh very often necessitates an increase in the dosage of insulin. Furthermore,
infection is usually accompanied by increased tissue catabolism resulting in the production of acid substances. Care must therefore be taken to meet occasional extra demands.

It is also wise in the provision of a dietary to give one with a high ash so that there may be an abundant supply of base.

In diabetic patients in the pre-insulin days operations under anaesthesia entailed so great a risk of acidosis and coma that surgical procedures were avoided if at all possible. To-day, however, it can be said that under careful supervision there is little if any added risk in operating on these patients. Whenever possible, the diabetic patient before being submitted to operative measures should be free of all manifestations of acidosis, have little or no glycosuria, and be in a good nutritional state. Glucose should be administered before, after, and, if prolonged, during the operation, so as to reduce to a minimum the formation of ketones. In short, it may be said that in the diabetic, whether affected by intercurrent disease or not, a properly adjusted diet and a sufficiency of insulin are the two essentials in the prevention of acidosis.

Coma.—Acidosis and coma are generally, but not invariably, preceded by a period of vague discomfort. The patient feels tired and drowsy and complains of headache and a feeling of sickness. Abdominal pain with or without vomiting is common. The temperature may be high or low, depending on the presence or absence of sepsis. Typical acidotic dyspnœa is a relatively late manifestation and should not be waited for before the diagnosis of acidosis is made. The breath smells of acetone and the urine contains large
amounts of this substance, although in rare cases it has been reported that acetonuria has not been present.

When coma supervenes, early and vigorous treatment is essential; it should be directed to the prevention of ketone-production and the restoration of the water and salt content of the body. Abundant insulin is usually sufficient to cause oxidation of the ketones, and a disappearance of acidosis. In order to ensure the presence of sufficient carbohydrate it is wise to give glucose simultaneously, especially if the diabetes has previously been untreated and there has been great depletion of carbohydrate. It is not the insulin per se but the increased utilisation of carbohydrate which leads to the disappearance of ketones.

**Rôle of Alkali in Treatment of Diabetic Coma.**—The administration of alkali is a subject on which there is still some difference of opinion. In pre-insulin days a recognised treatment for coma was the injection of sodium bicarbonate solution. With the advent of insulin there are many who urge that there is some danger associated with the simultaneous administration of alkali and insulin. Insulin treatment leads to an oxidation of the keto-acids so that the alkali which neutralised these acids has only carbon dioxide with which to combine. Accordingly with sudden increase of combined CO$_2$ an alkalosis may be produced. In incipient coma, which almost invariably reacts favourably to insulin therapy, it is unnecessary and probably unwise to give alkali, at any rate, intravenously. When, however, the coma has lasted for some hours, it is important to neutralise the excess of acids as soon as possible, and restore the reaction of the blood to its normal level. In such circumstances it is accordingly advisable to administer alkali intra-
venously, and thus effect an immediate rise in pH while the insulin is gradually restoring the carbohydrate metabolism to a more normal state.

**Figure IX**

**Showing the Diminution in Blood Volume During Diabetic Acidosis and Restoration After Recovery.**


Cases have been reported in which the carbon dioxide of the blood has remained low after the ketosis had been banished by insulin and glucose. In such
instances which may be due to excess production of non-ketone organic acids, the administration of alkali is necessary to produce a restoration of the normal acid-base equilibrium. The determination of the blood CO$_2$ or alkaline reserve is of great value as an index of progress in coma and as an indication for the necessity of alkali.

_Rôle of Water and Chlorine in Diabetic Coma._—Almost equally important with the supply of insulin and carbohydrate is the proper hydration of the tissues.

**Table VII**

SHOWING RISE IN BLOOD-CHLORINE IN DIABETIC PATIENT AFTER INGESTION OF GLUCOSE.

<table>
<thead>
<tr>
<th></th>
<th>Blood-Sugar mgm. per cent.</th>
<th>Blood-Chlorine mgm. per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ingestion of glucose.</td>
<td>303</td>
<td>156</td>
</tr>
<tr>
<td>One hour after ingestion of glucose.</td>
<td>531</td>
<td>248</td>
</tr>
</tbody>
</table>

It has already been mentioned that the combined diuretic effect of glucose and acidosis creates a state of dehydration which in turn leads to tissue destruction and further acid production. Determinations of the blood volume in diabetic acidosis indicate that the blood is concentrated and that with improvement there takes place a return to the normal blood volume (Figure IX). It is therefore of importance to supply fluid in ample amounts by the mouth or parenterally.

The chlorine content of the plasma is generally reduced as a result of its replacement by ketone acids,
the shift of chlorine from plasma to cells, and its excessive removal along with other electrolytes in the copious excretion of urine. Naturally, vomiting, if present, still further reduces the chlorine.

When the water content of the body is not unduly depleted there is generally enough extravascular chlorine available for union with the fixed base that has been freed from the keto-acids. Table VII illustrates the rise in blood chlorine after the administration of glucose to a diabetic patient.

The glucose presumably led to an oxidation of the keto-acids, thereby making available more base for union with chlorine.

It is well to remember, however, that the plasma chlorine does not necessarily give a true indication of the chlorine content of the body. As chlorine is held in solution by the tissue fluids, when these are diminished in quantity, there will be a diminution in total chlorine, though the chlorine of the plasma may remain comparatively high. So great may be the reduction in the total chlorine content of the body that in one instance 30 grammes of sodium chloride were given within twelve hours to an adult in severe diabetic acidosis without the production of hyperchloræmia or oedema (Peters and Van Slyke). This deficiency renders it advisable to give fluid in the form of saline. Otherwise, it is possible that with the oxidation and excretion of the ketones there will be left basic radicles which, owing to chlorine deficiency, will unite with carbonic acid and produce an alkalosis (Figure X).

A sufficiency of base is also ensured by giving saline, since the kidney excretes the excess chlorine as ammonium chloride and retains what base is required
ACIDOSIS AND ALKALOSIS

to unite with carbon dioxide. Hence the saline not only aids in the restoration of the normal bicarbonate content, but it prevents the accumulation of carbon dioxide in excess since the chlorine acts as a reserve acid which can be retained or excreted as necessary.

**Figure X**

**SHOWING BENEFICIAL EFFECT OF THE ADMINISTRATION OF SALINE ON THE COMPOSITION OF THE SERUM IN DIABETIC COMA.**

(Adapted from Peters and Van Slyke, *Quantitative Clinical Chemistry, Interpretations*, 1931, pp. 1056-8.)

<table>
<thead>
<tr>
<th></th>
<th>I. Normal.</th>
<th>II. Coma.</th>
<th>III. After treatment with insulin and glucose but no saline.</th>
<th>IV. After treatment with insulin, glucose and saline.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[Diagram showing composition of serum samples with changes in base, chlorine, and bicarbonate levels before and after treatment.]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note* the slight reduction in base and marked reduction in chlorine in II and III and the excess of carbonic acid in III, which is corrected in IV.
CHAPTER VIII

NEPHRITIS

The correlation of clinical, biochemical, and pathological findings in the various forms of nephritis is still beset with difficulties. For the purposes of the discussion of the disturbance in acid-base balance, it is sufficient to consider three main types: (1) the acute hæmorrhagic nephritis seen so commonly in childhood, (2) the chronic interstitial nephritis seen mainly in adults, and (3) nephrosis, which is characterised by massive albuminuria and œdema, and which may occur either in children or in adults. By most authorities it is now held that in the first two the principal defect is in the kidney itself, whereas in the third group there is probably an error in the general tissue metabolism.

Renal Function in Health.—The important part played by the kidney in maintaining a normal acid-base equilibrium has already been discussed (Chapter V). The principal functions of the kidney in this connection may be summed up as follows:

(1) Excretion of water. The maintenance of tissue water at a constant level has an important influence on the acid-base equilibrium, and if dehydration occurs, tissue breakdown becomes excessive, acid metabolites are formed, and acidosis is produced.

(2) Excretion of excess salts, acid and alkaline, to maintain the ionic concentration of the plasma and tissues at the normal level.

(3) Production of ammonia as a sparer of fixed base.
(4) Excretion of bicarbonate as an acid-sparer. When there is a deficiency of non-volatile acid, either relative or absolute, for neutralisation of base, the carbonic acid is held back in the tissue-fluids and blood in order to unite with the base, and, in consequence, is excreted in the urine as bicarbonate. On the other hand, as long as there is present in the body-fluids a sufficiency of non-volatile acid, bicarbonate does not appear in the urine since carbonic acid is readily expelled by the lungs.

**ACUTE HÆMORRHAGIC NEPHRITIS**

In general it may be said that in uncomplicated hæmorrhagic nephritis the changes in acid-base equilibrium are negligible. There are certainly no symptoms of any such disturbance. Blood analysis (Table VIII) shows that the carbon dioxide content varies within normal limits, but tends to be low.

### Table VIII

**SHOWING CHANGES IN CERTAIN BLOOD CONSTITUENTS IN THE VARIOUS TYPES OF NEPHRITIS.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>CO₂ Vol.</th>
<th>Cl. Mgm.%</th>
<th>N.P.N. Mgm.%</th>
<th>P. Mgm.%</th>
<th>Ca. Mgm.%</th>
<th>Fixed Base c.c. N/10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.E.</td>
<td>Acute nephritis (un-complicated).</td>
<td>45·5</td>
<td>295</td>
<td>56</td>
<td>4·0</td>
<td>8·9</td>
<td>150</td>
</tr>
<tr>
<td>F.E.</td>
<td>Acute nephritis with oedema.</td>
<td>49·7</td>
<td>320</td>
<td>48</td>
<td>6·0</td>
<td>9·8</td>
<td>149</td>
</tr>
<tr>
<td>F.B.</td>
<td>Acute nephritis with so-called ursæmia.</td>
<td>38·0</td>
<td>330</td>
<td>67</td>
<td>3·6</td>
<td>7·0</td>
<td>144</td>
</tr>
<tr>
<td>J.W.</td>
<td>Interstitial nephritis.</td>
<td>45·9</td>
<td>290</td>
<td>194</td>
<td>12·1</td>
<td>4·4</td>
<td>150</td>
</tr>
<tr>
<td>N.J.</td>
<td>Ursaemia.</td>
<td>20·6</td>
<td>285</td>
<td>343</td>
<td>16·0</td>
<td>3·7</td>
<td>—</td>
</tr>
<tr>
<td>A.B.</td>
<td>Nephrosis.</td>
<td>48·4</td>
<td>350</td>
<td>20</td>
<td>5·5</td>
<td>7·8</td>
<td>133</td>
</tr>
</tbody>
</table>

Determinations of CO₂, Cl, N.P.N. were made on whole blood; those of fixed base, calcium and phosphorus on serum.
Likewise, calcium and chlorine are, if anything, on the low side, although the former may be distinctly subnormal if the plasma protein is reduced, since normally about one-third of the serum calcium is bound to protein. Renal function, as measured by the ability of the kidney to form ammonia, varies considerably. In some cases ammonia production is scarcely impaired, whereas in others it is definitely diminished. In our experience, which agrees with that of most observers, function tests during the acute stage give no information regarding the ultimate prognosis. Similarly, analysis of the blood yields little information that is at present of value in prognosis or treatment.

Oedema.—Even with the well-marked oedema which occurs so frequently in the early stages of acute haemorrhagic nephritis, the acid-base balance is little if at all disturbed. The carbon dioxide content is generally unchanged, and the chlorine may be high or low. When oedema is very marked, there is a fall in the plasma protein which, as previously stated, will result in a lowered calcium content. It might also be mentioned that since, at the reaction of the blood, the protein acts as an acid, a diminution in the protein will tend to counteract any tendency to acidosis.

So-called Uræmic Convulsions.—It is particularly unfortunate that the term uræmia has become associated with the convulsions and coma that not infrequently occur in the early stages of acute haemorrhagic nephritis. Although the clinical picture may superficially resemble the true uræmia seen in chronic interstitial nephritis, ætiologically it is extremely doubtful if there is any relationship between the two conditions. Certainly the blood-chemistry, the prognosis and the immediate and ultimate results
of treatment are very different. It has been suggested that these convulsions would be better termed the cerebral manifestations of acute nephritis, as the causal factor is probably cerebral œdema. When the œdema is relieved, recovery as a rule rapidly ensues, leaving no apparent permanent injury either to the kidney or to the central nervous system.

The non-protein nitrogen (or blood urea) is either normal or only slightly increased, thus contrasting with the well-marked nitrogen retention seen so constantly in true uræmia. The carbon dioxide content of the blood is, as a rule, reduced, as is also the pH. It has recently been suggested that to some extent at any rate, this lowering of the pH is the result of accumulation of lactic acid, following on the anoxæmia produced by the convulsions. This is of importance since it suggests that the acidosis is a sequel and not a cause of the convulsions and from a practical point of view renders it unnecessary to adopt any measures to counteract the acidosis.

**CHRONIC INTERSTITIAL NEPHRITIS**

In this condition there is a great impairment of the ability of the kidney to excrete nitrogenous waste products (nitrogen retention), many of which are acid, and of its power to form ammonia. Accordingly, there is an excessive call on the fixed base of the body for the neutralisation and excretion of acid. Should this supply of base become defective, the acid radicles accumulate in the blood and tissue-fluids, the available alkali becomes used up, and a non-gaseous acidosis is produced. It is apparent, then, that the acidosis of chronic interstitial nephritis differs from that of
diabetes: in the latter, acids are formed in excess in the tissues, whilst in the former, neutralisation and excretion of acids are at fault.

**Blood Chemistry** (Table VIII).—There is throughout the course of the disease some degree of nitrogen retention (azotemia) as evidenced by the high blood urea and non-protein nitrogen contents of the blood. In marked cases the blood carbon dioxide content may fall below normal. In the less severe cases it is not much diminished, although there is always present a "potential" acidosis, for it can be shown that even in these the mechanism for controlling acid-base equilibrium is to a certain extent always overtaxed. Thus, for the neutralisation and excretion of acid products in the urine there is a continual demand on the fixed base, which may therefore be reduced in the blood. The chlorine content is also frequently diminished, its diminution, as a rule, going parallel with that of fixed base. The inorganic phosphate and sulphate of the serum are generally raised, as are also such substances as uric acid, creatine, creatinine, and amino-acids. In fact, these substances, mainly acid in character, are all held up in the blood because of the inability of the kidney to excrete them, the degree of retention being a rough guide to the severity of the damage to the kidney function.

The deficit in the fixed base of the serum is almost entirely restricted to sodium and calcium, the potassium remaining unchanged. This is due to the fact that sodium and calcium are chiefly found in the extracellular fluids while potassium is an intracellular element. The withdrawal of these extracellular fluids, then, will not affect the potassium. Indeed, the potassium in the blood may occasionally be increased
ACIDOSIS AND ALKALOSIS

as a result of breakdown of tissues. A low serum calcium value is a common finding in severe cases of interstitial nephritis. Its amount varies inversely with that of the serum phosphorus, and it is more than

**FIGURE XI (a)**

SHOWING THE VARIATIONS IN URINARY VOLUME AND OF CERTAIN URINARY CONSTITUENTS DURING A TWENTY-FOUR HOUR PERIOD. THE CALORIC INTAKE PER KILO BODY WEIGHT IN EACH CHILD WAS IDENTICAL IN AMOUNT, QUALITY, AND DISTRIBUTION.

(A) HEALTHY CHILD

![Graph showing variations in urinary volume and certain urinary constituents during a twenty-four hour period.](image-url)
probable that the rise in the phosphorus is an important factor in the production of the serum calcium deficiency. Such a fall in calcium is seldom associated with tetany, as the acidosis present counteracts this by ensuring an adequate supply of ionised calcium. In one instance, however, we have noted the presence of a well-marked facial phenomenon, but without other signs of tetany.

**Urine.**—In the advanced cases of interstitial nephritis the concentrations of the various substances

**FIGURE XI (b)**

**SHOWING THE VARIATIONS IN URINARY VOLUME AND OF CERTAIN URINARY CONSTITUENTS DURING A TWENTY-FOUR HOUR PERIOD. THE CALORIC INTAKE PER KILO BODY WEIGHT IN EACH CHILD WAS IDENTICAL IN AMOUNT, QUALITY, AND DISTRIBUTION.**

*(B) CHRONIC INTERSTITIAL NEPHRITIS (RENAL DWARF).*
excreted in the urine remain remarkably constant from hour to hour (compare Figure XI, (a) and (b). Ingestion of food does not alter the composition of the urine to anything like the same extent as it does in the normal subject. The first renal function to be impaired is probably ammonia formation. The production of an acidosis by the use of calcium chloride, for example, in

**Table IX**

**SHOWING CHANGES BROUGHT ABOUT IN THE URINE BY THE PRODUCTION OF AN ACIDOSIS BY MEANS OF CALCIUM CHLORIDE.**

<table>
<thead>
<tr>
<th></th>
<th>Titratable Acidity. c.c. N/10 per day.</th>
<th>Ammonia. c.c. N/10 per day.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per. I</td>
<td>Per. II</td>
</tr>
<tr>
<td>Normal</td>
<td>239</td>
<td>305</td>
</tr>
<tr>
<td>Chronic interstitial nephritis (advanced)</td>
<td>142</td>
<td>84</td>
</tr>
<tr>
<td>Nephrosis</td>
<td>259</td>
<td>205</td>
</tr>
</tbody>
</table>

Diets during both periods were identical, but during period II calcium chloride (gm. 2, four-hourly) was ingested.

such cases does not result in the normal increased ammonia production (Table IX); possibly the urea concentrating power is simultaneously impaired, but this does not play any direct part in the regulation of acid-base equilibrium. It is only later that the power to excrete weak un-neutralised acid, as represented by the titratable acidity, is affected. The result of this is that the ratio \( \frac{\text{c.c. N/10 ammonia}}{\text{c.c. N/10 titratable acid}} \) is frequently
NEPHRITIS
decreased in early nephritis, since the impairment of ammonia production is usually greater than any defect there may be in the excretion of weak acid. The ammonia coefficient likewise will not show an increase as it does, for example, in the acidosis of diabetic coma where the power of the kidney to form ammonia is quite unimpaired. The amount of organic

**Table X**

**SHOWING OUTPUT AND RETENTION OF CALCIUM AND PHOSPHORUS IN HEALTH AND CHRONIC INTERSTITIAL NEPHRITIS (RENAL DWARFISM).**

(Data obtained from Dr. F. J. Ford, Royal Hospital for Sick Children, Glasgow.)

<table>
<thead>
<tr>
<th></th>
<th>Calcium.</th>
<th>Phosphorus.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intake CaO gm. per day.</td>
<td>Intake P₃O₅ gm. per day.</td>
</tr>
<tr>
<td></td>
<td>Retention CaO gm. per kg. per day.</td>
<td>Retention P₃O₅ gm. per kg. per day.</td>
</tr>
<tr>
<td>Normal.</td>
<td>3.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Chronic Interstitial Nephritis.</td>
<td>2.7</td>
<td>3.78</td>
</tr>
</tbody>
</table>

acid in the urine is also diminished: probably more is oxidised in the body because of the deficiency of base. For these reasons, then, one must conclude that there is in the subject with chronic interstitial nephritis a condition of "potential acidosis."

The urinary output of calcium and phosphorus is greatly diminished (Table X). Actually, too, the retention of these two substances is below normal, excessive amounts being excreted in the faeces. This may be a very serious feature in young children. It
may lead to defective growth and osteoporosis (renal dwarfism). When growth occurs, owing to diminished retention of minerals, the condition known as renal rickets arises. It has been shown that absorption is at least as good as in normal individuals, which would indicate that there is excessive re-excretion of minerals into the bowel. In nephritis the poor retention of calcium and phosphorus seems to be associated with the impaired kidney function.

**Uraemia in Chronic Interstitial Nephritis.**—In uraemia we have an intensification of all the factors mentioned above, although actually the cause of the coma is still uncertain. The disturbances in acid-base balance are readily traced back to the inefficiency of the kidney in forming ammonia and the consequent difficulty of excreting acid.

It has been suggested that, owing to the diminished urinary excretion of phosphorus, phosphate accumulates in the blood and is the cause of the acidosis. In the first place, far from there being an excess there is a diminution in the retention of phosphorus. The greatest increase in inorganic phosphate of the plasma that we have found, amounted to 13 mgm. per 100 c.c., which is the equivalent of 7·6 c.c. N/10 acid per 100 c.c., and therefore can only account for 17·0 volumes per cent. of carbon dioxide. An increase in serum phosphorus of much less than 13 mgm. per cent. is frequently accompanied by a reduction in carbon dioxide, amounting to more than 20 volumes per cent. Also, the administration of alkaline sodium phosphate (Na₂HPO₄) to a nephritic subject with a high serum phosphate and low carbon dioxide content has led to a restoration of the carbon dioxide to normal, although the serum phosphate remained high. Therefore, factors
in addition to phosphate accumulation must be responsible for the acidosis. In point of fact, both the high phosphorus and low carbon dioxide must be due to a common underlying cause.

It is believed by some that the acidosis of nephritis may be traced to excess retention of chlorine. Occasionally high chlorine contents of the blood and the plasma have been noted, but generally, the acidotic state of chronic nephritis is associated with a diminution in plasma chlorine. There has also been noted a "dry retention" of chlorine, i.e. without a corresponding retention of water. This, however, has been denied by Peters, Wakeman, and Lee, who maintain that the hypochloræmia so frequently found in advanced nephritis is due to the tendency of base and chlorine to be excreted in the urine even when plasma chlorine is below the normal threshold value. In one instance these workers found an excess loss of chlorine in the fæces, although the sodium chloride was given subcutaneously, and there was no diarrhœa. It is possible, however, that the ability of the kidney to excrete chlorine is a factor of considerable importance in saving the organism from acidosis. By the elimination of chlorine a strong acid is replaced in the tissues by a weak one, which affects the acid-base balance to a much less extent. In connection with the metabolism of chlorine the fact that lack of chlorine may lead to an increase in the non-protein nitrogen content of the blood is worthy of mention. This is of importance in the use of the non-protein nitrogen as a guide to prognosis and treatment, since a high value may be due to deficiency of chlorine and may be quickly reduced to a much lower level by the administration of sodium chloride.
Dehydration.—It has long been known that patients with chronic interstitial nephritis readily become dehydrated. Restriction of fluid intake in these patients does not lead to an immediate reduction in the volume of urine as in health. Polyuria may continue for several days, and with the fluid there is also lost a considerable amount of salt. The state of dehydration produces breakdown of tissue substance. Phosphorus, uric acid, and other organic acids accumulate in the blood-plasma and tissue fluids: the carbon dioxide of the blood is partially displaced by these from its union with base and a state of non-gaseous acidosis is produced. The acidosis may be further enhanced by deficiency in fixed base much of which may have been excreted in the urine in combination with acid metabolites.

Reduction of the carbon dioxide content of the blood is probably a fairly reliable guide to the extent of the acidosis prevailing in interstitial nephritis. The fall in carbon dioxide may be associated with one or more of the following: (1) low plasma base, (2) high inorganic phosphate, and (3) high organic acid content of the blood (ketones, etc.). The total acid only exceeds normal limits when the organic acid is greatly increased. This latter occurrence takes place with excessive vomiting, carbohydrate starvation, or dehydration. When the supply of carbohydrate is deficient the excess organic acid is mainly ketone, but in the other conditions the organic acid falls into the group of undetermined acid. Excess of phosphate, sulphate, and other acid radicals may explain the slight degree of acidosis associated with a blood carbon dioxide bordering on the lower limits of normal. It is, however, to the kidneys' inability to regulate water
and salt loss that must be attributed the dehydration which, with the inability to form ammonia, is the potent cause of the acidosis found with chronic interstitial nephritis. The more severe the nephritis, the more delicate must be the adjustment between the water and salt intake. Too much water will deplete the body of its salt content, as an increased urinary output will carry an increased amount of salt with it. On the other hand, if salt be given in excess, the tissue fluid will be diminished since the water is required to excrete the salt.

**Effect of Acid and Alkali Administration.**—As one would expect in subjects suffering from chronic interstitial nephritis, the kidneys do not react well to the ingestion of acid substances. The figures (Table IX) illustrate clearly the defective rise in the output of ammonia and titratable acid when an acid-producing salt such as calcium chloride is given to a patient with chronic nephritis.

The administration of alkali relieves the situation to some extent, but curiously enough alkali may lead to an excessive amount of carbon dioxide in the blood, although the urine remains acid. This we have not observed personally in chronic nephritis, but it is not an uncommon occurrence in pyuria. Ellis has reported definite bicarbonate excess, and a high pH of the serum of a chronic nephritic, although the urine was acid. This suggests defective bicarbonate excretion by the kidney, and it is possible in such cases that the kidney is only able to secrete a urine, the pH of which varies within comparatively narrow limits. Peters and Van Slyke, on the other hand, attribute this state of affairs to deficiency of the fixed base of the plasma, any base absorbed being retained as bicarbonate.
ACIDOSIS AND ALKALOSIS

Nephrosis

Under this heading are included those patients with massive albuminuria and chronic oedema classified either as nephrosis or parenchymatous nephritis.

Blood Chemistry.—A deficiency in the plasma protein is the significant and, apart from the rise in blood cholesterol, the only characteristic abnormality in the blood chemistry. Because of the base-binding properties of protein, the fact that it is lowered must have some influence on acid-base equilibrium. Cholesterol metabolism is not discussed here since it does not appear to have a direct bearing on disturbances of acid-base equilibrium. There is no nitrogen retention; the blood urea and non-protein nitrogen, the inorganic phosphate and sulphate, and the organic acids remain unaltered. Not uncommonly, the chlorine is raised. The fixed base varies in amount, but is more often below than above normal limits, the calcium, especially if the protein be greatly diminished, being definitely below normal. The carbon dioxide content of the blood is usually unchanged, but this is dependent upon the changes in chlorine, fixed base, and protein.

Urine.—The ability of the kidney to form ammonia is unimpaired (Table IX), although the total amount may be low owing to the diminished amount of water excreted. There would appear to be some interference with the ability of the kidney to excrete water, fixed base, and chlorine. It is not yet decided which of these is primarily affected. Peters and his colleagues have found that, after the ingestion of ammonium chloride, there is a tendency to excessive chlorine retention with but little diuretic response. They conclude that the subject with this hydremic type of
NEPHRITIS

kidney disease has a special difficulty in excreting chlorine. We have found that the use of a non-chlorine acid-producing salt such as ammonium sulphate (\(\text{NH}_4\text{SO}_4\)) led to an increase of chlorine in the blood, but with little effect on the amount of chlorine excreted in the urine. It is quite possible, therefore, that a rise in the blood chlorine is the result of the action of an acid-producing substance, whether containing chlorine or not.

GENERAL ASPECTS OF TREATMENT

From a consideration of the foregoing, several indications for treatment become apparent.

\textit{Hæmorrhagic Nephritis.}—Acid-base disturbance is not a feature of this form of nephritis, and the slight degree of acidosis which may be present can be neglected. As has been pointed out, the signs of the so-called uræmia which occur in this condition are probably related to cerebral oedema, and not to acidosis. In the comatose patient with convulsions, blood-letting, withdrawal of spinal fluid, hot packs, or the use of one per cent. magnesium sulphate intravenously and orally are usually successful, the accompanying acidosis righting itself almost immediately. It is seldom, if ever, necessary to give alkali in these cases.

Osman, however, in all cases of acute nephritis, has recommended the giving of massive doses of alkali, especially if there is marked oedema. The alkali is to be given in increasing amounts, even although the oedema is increasing. Later, a sudden change is said to take place, and a copious diuresis occurs. One must, however, remember that not infrequently diuresis sets
in spontaneously, and the value of the various forms of treatment becomes very difficult to assess. One point to be remembered in the alkali treatment is the possibility of the development of tetany as a result of the alkalosis so induced. This which we have observed in one case, is readily dealt with, of course, by withdrawal of the alkali.

**Chronic Interstitial Nephritis.**—In this (the azotemic form), there is a very good reason for adopting the alkaline treatment, or at least for giving the patient an alkaline diet rather than an acidic one (see Appendix I). Lyon, Dunlop, and Stewart, however, point out the advantages of giving a diet containing a more adequate supply of protein than is usually advised in chronic nephritis, and recommend a diet with ample protein in addition to the administration of alkali. By this, the carbon dioxide content of the blood is kept up, while the non-protein nitrogen falls to a lower level. The excretion of urea also seems to be favourably influenced, although the elimination of other substances, such as creatinine, is not altered. The advantage of an adequate protein intake is to spare the tissue protoplasm and thus prevent its excessive catabolism, but the beneficial effect produced on the acid-base equilibrium is entirely due to the alkaline nature of the diet. Figure XII illustrates how dramatic the effect of an “alkaline diet” may be on the blood chemistry in chronic interstitial nephritis.

**Nephrosis.**—Here, there are three facts of importance to guide us in the treatment, namely, the deficiency in plasma proteins, the efficiency of the kidney in forming ammonia and the difficulty in the excretion of water and inorganic substances. Accordingly three therapeutic measures are indicated:
NEPHRITIS

(1) A dietary rich in protein (meat, fish, eggs, etc.).

(2) A dietary poor in ash.

(3) The administration of an acid-producing substance. The high protein intake will enrich the depleted plasma protein, and the portion completely catalysed can be readily dealt with by the kidney, as

**Figure XII**

**SHOWING THE EFFECT OF AN ALKALINE DIET ON THE BLOOD CHEMISTRY IN CHRONIC INTERSTITIAL NEPHRITIS.**

(Data obtained from Dr. F. J. Ford, Royal Hospital for Sick Children, Glasgow.)

...ammonia formation is unimpaired. A diet of this nature is acid-producing and, fortified by an acid-producing salt, will tend to induce a flow of fluid from the tissue spaces to the plasma and thence to the kidney for excretion. A low ash diet is clearly indicated because of the inability to excrete minerals, which are retained in solution and lead to an increase of the tissue-fluids with consequent increase in œdema.
In practice, mixed types of nephritis are frequently found and particularly is this so in childhood. For this reason the indications for treatment are often contradictory and confused. The most important and an easily ascertained point of differentiation is the ability of the kidney to form ammonia. When this function is impaired a diet containing an excess of alkali is of advantage. If ammonia formation is normal, and especially if oedema is present, an acid diet would appear to be indicated.
CHAPTER IX

GASTRO-ENTERITIS

The syndrome of diarrhoea and vomiting in infants and young children, whether due to enteral or parenteral causes, is very frequently associated with disturbances in acid-base equilibrium. In the more severe forms of gastro-enteritis the upset in acid-base balance may actually dominate the clinical picture and, because of its extreme urgency, demand immediate therapeutic measures. It is, therefore, of the utmost importance to understand the pathological processes leading to the development of acid-base disturbance in order to provide treatment that will efficiently neutralise the effects and prevent the development of these active pathogenic processes.

In a moderately severe case of gastro-enteritis we are concerned with four different processes: (1) vomiting, (2) diarrhoea, (3) inanition, partial or complete, and (4) bacterial infection.

Vomiting.—The effect of vomiting is to produce a loss of gastric secretion and limit the intake of food. The gastric secretion of healthy infants contains less free hydrochloric acid than that of older children. In all types of infection, but especially when any part of the alimentary tract is involved, the secretion of hydrochloric acid becomes greatly diminished. Accordingly, the loss of chlorine produced by vomiting is, in gastro-enteritis, practically always balanced by a loss
of fixed base. The main effect of vomiting, therefore, is the loss of fluid with its associated acid and base.

**Diarrhoea.**—Diarrhoea, on the other hand, while also leading to a very marked loss of water, is associated with an excessive loss of alkaline substances. The base thus lost comes in part from the food which is hurried through the alimentary tract and in part from the intestinal secretions. Indeed, in the motions obtained from infants with severe diarrhoea, more sodium has been found than has been ingested. This is due to the fact that the alimentary secretions below the pylorus are relatively very rich in base, bound to
carbonic acid as bicarbonate (Figure XIII). It is clear that excessive loss of pancreatic juice and bile will result in much greater withdrawal of base as bicarbonate than as chloride. Experimental investigations have shown that following continuous removal of the intestinal secretions by means of a fistula, there has resulted a reduction in the fixed base of the plasma. Furthermore, irritation of the bowel wall by inflammatory processes may also lead to the loss of fluid containing a considerable amount of inorganic substances.

Figure XIV gives a graphic representation of data of Holt, Courtney and Fales, showing the ratio of
fixed acid to fixed base in normal, loose, and very loose stools. It is clear that although the ratio is practically unchanged even in acute diarrhoea, the actual faecal loss of base in excess of acid is very great, necessitating the excretion of a correspondingly greater amount of acid by the kidney. Owing to the poor supply of water at the disposal of the kidneys and consequent inability to excrete these acids, there may result an unbalanced accumulation in the body of acid substances. In diarrhoea, therefore, the loss of water, together with salts, preponderantly alkaline in nature, results in an excess of acid substances accumulating in the blood and tissue-fluids.

**Inanition.**—Inanition is accompanied by the breakdown of tissue fat and protein since the reserve of carbohydrate, the glycogen in the liver and muscles, soon becomes exhausted in the young child. This naturally entails not only the formation and circulation of keto-acids resulting from the disturbed fat metabolism, but probably also of other acid bodies derived from the proteins. The breakdown of tissue substance is further intensified by the excessive loss of water in the vomitus and stool. The bicarbonate content of the blood is lowered, the urine becomes very acid with large amounts of acid phosphate and ammonia, and simultaneously there occurs, owing to the acidosis so produced, a further call on the body fluids with resulting dehydration and decrease in blood-volume. The breakdown of tissue substance is shown by the presence of considerable amounts of potassium (an intracellular base) in the urine.

**Bacterial Infection.**—Bacterial infection stimulates all catabolic processes with the consequent disturbance of carbohydrate metabolism and the formation
of excess acid. This superimposed on a body already poor in reserve water and foodstuffs aggravates still further the condition of acidosis.

The net result of all these processes is the loss of water, the loss of alkali but relatively little acid and the excessive production of organic acids. It will be remembered that the two important defences against an excess of acid are, first, the available alkali of the blood and tissues, and second, the power of the kidney to excrete acid substances. The supply of alkali is depleted by the loss of base through the bowel as is indicated by the diminution of fixed base of the plasma, especially sodium. The available alkali left, i.e. that portion combined with carbon dioxide, is rapidly used up so that in severe cases of gastro-enteritis one meets with extremely low values for the alkaline reserve. The power of the kidney to excrete acid substances is greatly diminished as a result of the very small amount of water left for formation of urine. This deficiency in urinary volume naturally results in the excretion of smaller amounts of free acid and the formation of smaller amounts of ammonia. Accordingly, there is produced an acidosis of the non-gaseous type showing the usual signs, namely, an increased volume of breathing, a lowered alkaline reserve, and a decrease in the pH of the blood. An associated phenomenon is that of marked dehydration characterised by dryness and loss of elasticity of the skin.

The blood also loses water (anhydræmia), with the result that it becomes thicker and more viscous. Accordingly, the blood-flow becomes slower, and the oxidation and general exchange of metabolism is depressed, which will further accentuate the acidotic condition.
ASPECTS OF TREATMENT

Therapeutic measures must be directed towards securing (1) a normal water content, (2) prevention of further loss of base and a restoration of the reserve of alkali, (3) the cessation of excessive acid formation, and (4) a return to normal of the pH. The reasons why a normal water content should be secured are that minerals cannot be stored nor tissue anabolised without water, that deficiency of water itself, by increasing catabolism, will cause an acidosis and that a plentiful supply of water is required for efficient renal function.

To accomplish these objects fluid must be given in abundance. If vomiting is not troublesome and the condition not acute, oral administration may be sufficient. In all cases where the vomiting is troublesome and in all severely dehydrated infants, fluids must be given parenterally, either intravenously, intraperitoneally, or subcutaneously. The fluid should be given as some form of saline solution (see Appendix II), in order to preserve the osmotic equilibrium and supply the necessary inorganic substances. Gastric lavage, when adopted as a method of treatment, should be performed with sodium bicarbonate solution (1 per cent.) and some of the solution left in the stomach.

Many of the acid substances resulting from excessive tissue catabolism are formed because of the lack of carbohydrate. Accordingly, it is advisable to supply this in a form easily utilised, namely, glucose. The oxidation of glucose prevents the formation of ketoacids, and has the further advantage that it leads to the storage of water. The combination of 10 per cent. glucose with normal saline we have found to be a
GASTRO-ENTERITIS

particularly useful form for intravenous therapy. Normal saline alone is advisable when the intraperitoneal route is being used because of the risk of infection in introducing a solution of glucose in such close proximity to the bowel. The administration of insulin together with glucose is sometimes recommended, but we have found no benefit ensuing from this procedure, except, possibly, the prevention of a slight overflow glycosuria.

Alkali may be given to infants with very marked signs of acidosis, but should never be administered intravenously with glucose, since the latter reacts with the alkali to form toxic substances. Hartmann has shown that the acidosis of gastro-enteritis is often accompanied by hyperchloremia, which he attributes to the fact that much more base is lost than chlorine. He therefore suggests that the administration of alkali or alkali-producing substances, such as sodium lactate, is always required. Hoag and Marples, however, maintain that, provided an abundance of sodium chloride solution is given, the deficiency of base is rapidly made good. The action of the saline is suggested by Peters and Van Slyke to be as follows:

\[(\text{NH}_4\text{HCO}_3) + \text{NaCl} \rightarrow \text{NH}_4\text{Cl} + \text{NaHCO}_3\]

The important point is that sufficient fluid must be given to cause a fairly copious diuresis so that the tissues may be properly hydrated and the kidneys supplied with ample water for the excretion of waste-products.

By these measures it is possible to arrest the progress of acidosis and dehydration, and cause a return to normal conditions of osmotic and acid-base
equilibrium. This, although admittedly symptomatic treatment, allows time for the institution of therapeutic measures to deal with the causes of the diarrhoea and vomiting.

Blood transfusion has been used but, except when there are signs of collapse, it has, in our hands, not proved superior to treatment with glucose and saline. Indeed, if the blood is concentrated to any extent, blood transfusion may be actually harmful.

The improvement in the general condition of the patient usually forms the best index of the efficacy of treatment. If it is desired to obtain a quantitative measure of the effect of therapy so far as acidosis is concerned, the best test is the value for the total carbon dioxide of the blood or the alkaline reserve.
CHAPTER X

CYCLICAL VOMITING

By cyclical vomiting one understands the condition in which there occur periodic attacks of severe vomiting, sudden in onset and associated with a well-marked ketonuria. There is frequently fever, but seldom is this alarmingly high, and although the general condition of the patient may be such as to cause considerable anxiety, a fatal termination is fortunately not common. The cessation of the vomiting and the rapid convalescence of the child is as dramatic as the suddenness of onset. Between attacks normal health is enjoyed. In rare cases the vomiting is not a prominent feature, although the appearance of the patient may be no less alarming. In other cases each attack may be associated with what appears to be a respiratory infection, its periodicity and response to treatment giving the clue to the proper diagnosis. On the whole, the condition tends to occur in better-class children, particularly in the "only child."

Investigations into the chemical pathology of this condition are extremely difficult, not because of its rarity, since it is comparatively common, but because of the curious fact that such children when brought under observation in a hospital ward fail to have attacks in much the same way as many children with epilepsy will remain free from attacks while under hospital régime. We have in only one instance
succeeded in obtaining observations just before and during a complete attack.

In every case deserving of a diagnosis of cyclical vomiting, there is present an acidosis, of a non-gaseous or acid-poisoning type. In the classical case, the patient is acutely ill, dehydration is present as evidenced by the sunken eyes and retracted abdomen, and there is usually well-marked air-hunger, the intensity of which is proportionate to the severity of the acidosis: cyanosis is absent. Constipation is usually present, although diarrhoea may occur. Abundant ketone bodies are present in the urine, sometimes a few hours before the onset of the vomiting, and the characteristic sweet breath of such patients, due to the acetone being given off by respiration, is readily recognisable. Occasionally with severe renal impairment it is possible that acetone may be absent from the urine just as has been described in rare cases of diabetic coma. Some type of abdominal pain is frequently present, most often epigastric in situation, but sometimes in the lower abdomen and not infrequently the vomiting and abdominal pain have led to a diagnosis of appendicitis and a consequent laparotomy under general anaesthesia—a procedure of considerable danger in the presence of a severe acidosis.

Examination of the blood reveals a lowered carbon dioxide content (often as low as 18–20 vol. per cent.) and a normal or slightly increased chlorine content. The urine is strongly acid, and its ammonia content is high. Rothera’s test for acetone bodies is strongly positive. The vomitus contains abundant chloride, but no free hydrochloric acid. Between attacks the total carbon dioxide content of the blood will be found normal.
The production of acidosis during a period of good health does not precipitate an attack. Such an acidosis may be produced by the administration of an acid-producing salt, e.g. calcium chloride or ammonium chloride, or by means of a ketogenic diet. Although the blood carbon dioxide is reduced and abundant ketones appear in the urine of those children on ketogenic diets, no vomiting ensues, and, clinically, there is no resemblance to an attack of cyclical vomiting. Indeed, the child looks quite well.

We have been fortunate in observing throughout a complete attack one patient (E. G.) under the care of Dr. Leonard Findlay. Her case history seems to us to throw some light on the metabolic processes concerned.

Case I.—E. G., female, aged eight years and three months. Normal birth and development till one year, when she had an attack of diarrhoea and vomiting lasting six weeks. Chickenpox at three years: mumps at four years. Otherwise healthy till five years, when she had a severe attack of measles. Since then, bouts of diarrhoea and vomiting lasting about one week and recurring every three months. During an attack she is feverish and very thirsty. After the diarrhoea and vomiting have ceased recovery is rapid.

15.10.20.—Admitted during attack: slight fever (100.4).

**Blood.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total carbon dioxide</td>
<td>38.6 volumes per cent.</td>
</tr>
<tr>
<td>Chlorine</td>
<td>400.0 mgm. per cent.</td>
</tr>
<tr>
<td>Non-protein nitrogen</td>
<td>59.8 mgm. per cent.</td>
</tr>
<tr>
<td>Van den Bergh reaction</td>
<td>Indirect strongly positive</td>
</tr>
</tbody>
</table>

**Urine.**

- Reaction acid, acetone + + +, urobilin +.
- Lävulose Tolerance Test.
  (Blood-sugar curve after administration of one gramme lävulose per kg. body weight.)

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Blood sugar (mgm. per cent.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>72</td>
</tr>
<tr>
<td>60</td>
<td>147</td>
</tr>
<tr>
<td>90</td>
<td>261</td>
</tr>
<tr>
<td>120</td>
<td>134</td>
</tr>
</tbody>
</table>
30.10.29.—Dismissed well.
12.5.30.—Was re-admitted to test the effect of ketogenic diet.
13.5.30.—Before ketogenic diet was given child looked “seedy.”

_Blood_ at 10 a.m.
- Total carbon dioxide .. .. . 36.6 volumes per cent.
- Sugar .. .. .. .. 72 mgm. per cent.

_Urine_ contained no acetone.

At 4 p.m. she vomited once. A specimen of urine obtained at this time contained fairly abundant acetone and the breath smelt strongly of acetone.

14.5.30.

_Blood._
- Total carbon dioxide .. .. 35.6 volumes per cent.
- Sugar .. .. .. .. 64 mgm. per cent.

No vomiting. Put on ketogenic diet.

15.5.30.—Looks better this morning.

_Urine_ acetone + + +.

17.5.30.—Child seems quite well.

_Blood._
- Total carbon dioxide .. .. 34.9 volumes per cent.
- Sugar .. .. .. .. 58 mgm. per cent.

A consideration of the findings in this case brings out the following points. Firstly, the onset of acidosis as judged by the low carbon dioxide content of the blood and the appearance of ketonuria occurred before there was any vomiting. The vomiting then is probably the result and not the cause. This seems to be the more likely sequence of events. Vomiting when primary usually results in an alkalosis from loss of chlorine, and the production of an acidosis in this circumstance would be inexplicable. Secondly, the ammonia coefficient did not rise much until the end of the attack. The failure of this defensive mechanism to come into play sooner undoubtedly aggravated the acidosis. One has always to keep in mind a relative failure of one of the defences against acidosis. Thirdly, the fasting blood-sugar was not unduly low: in fact, it tended to fall as the condition of the patient improved.
Hypoglycæmia, as has been suggested by some, was not a factor here. The statement has been made that those children who suffer from attacks of cyclical vomiting show a much more rapid and marked fall in blood-sugar and more intense ketosis during inanition than do normal children. This has certainly not been our experience, and we feel that the theory that hypoglycæmia is an important ætiological factor has
had no serious confirmation. Lastly, as previously mentioned regarding ketogenic diets, the ingestion of a ketogenic diet, although accompanied by a low carbon dioxide of the blood and the excessive production of acetone bodies, was not associated with vomiting or any other symptom of an attack of cyclical vomiting.

We would suggest that the cause of cyclical vomiting is a temporary impairment of hepatic function, and from the above observations this view is strengthened by the finding of a positive l-aevulose test and the presence of excess urobilin in the blood and urine during the attack on the first admission. The vomiting is effect and not cause, and is probably due to the temporary inability of the liver to deal with the excess of ketones. The ketones are, of course, the product of incomplete combustion of the fats. In the quiescent intervals fat metabolism is normal, but periodically, due possibly to some nervous or psychological cause, there is a sudden call on the store of glycogen, and, in the attempt to deal with large amounts of fat brought in to replace the sugar, the liver function breaks down and an attack occurs with its attendant vomiting and acetonæmia.

Associated with this impaired or overburdened hepatic function, there may be as well, some impaired renal function, although it must be admitted that the increase in ammonia production in the case quoted was only slightly delayed (compare Figure XV and Figure XVIII).

**TREATMENT**

The treatment of cyclical vomiting is most rationally that of prevention. Children subject to this condition should be given a low fat, high carbohydrate diet, so
that any failure of fat combustion because of lack of sugar is prevented as far as possible. In most instances, however, this is not sufficient and it will be found that a daily dose of alkali (half a teaspoonful of baking-soda) is advisable. Such a régime in the great majority of instances will cause a cessation of the attacks. If a considerable reduction in the fat intake is necessary the resulting vitamin deficiency (A and D) should be made good.

The actual treatment of an attack must be directed to three objectives: (1) prevention of the formation of more acid bodies, (2) neutralisation and excretion of acid substances already produced, and (3) replacement of the water lost by vomiting. These can often be achieved by the judicious administration of glucose and sodium bicarbonate, and abundant water by the mouth. Glucose in a 10 per cent. solution intravenously is to be strongly recommended in very severe cases. It is seldom, if ever, necessary to give alkali intravenously, and we would again emphasise the danger of combining glucose and sodium bicarbonate for intravenous injection. In milder cases, if not retained by mouth, glucose may be given per rectum. In fact, since many of these children are constipated, it is wise as a routine to clear the bowel by enema and give rectal glucose. The glucose prevents the formation of ketone bodies and accelerates their combustion, while the alkali rapidly makes good the loss of base and raises the plasma carbon dioxide.

**AN ALKALOTIC TYPE OF CYCLICAL VOMITING**

Such a case as described on page 142 (G. S., Chapter XIV), might be considered a typical example of
periodic attacks of vomiting occurring with changes exactly opposite to those seen in non-gaseous acidosis, namely, non-gaseous alkalosis. In these cases the breathing is slow and shallow in contrast to the acidotic type, while the carbon dioxide is high, and the chlorine of the blood and urine is diminished. In the case quoted the urine remained acid, this again suggesting a renal factor—a kidney unable to excrete excess of base as bicarbonate.

In these cases the stomach is always dilated, and vomiting is the primary factor concerned in the production of the acid-base disturbance, frequently leading to the onset of gastric tetany.

**Treatment.**—Since the loss of chlorine in the vomitus is the immediate cause of the alkalosis, this must be made good. The administration of sodium chloride in large amounts is the most valuable form of treatment. Where tetany is present, an acid-producing substance containing chlorine (calcium chloride, ammonium chloride, or hydrochloric acid), is indicated. Certain cases may lend themselves to surgical procedures.
CHAPTER XI

KETOSIS AND KETOGENIC DIET

Significance of Ketosis.—It has already been pointed out that the word ketosis signifies merely an accumulation of ketones in abnormal amounts in the body. The three terms, ketosis, ketonæmia (acetonæmia) and ketonuria (acetonuria), are for all practical purposes synonymous, these conditions being recognised clinically by the presence of a positive Rothera’s test in the urine.

Much confusion exists as to the exact significance to be attached to the appearance of ketone bodies in the urine. Indeed, it is not unusual for this to be looked upon as indicating a state of acidosis, an interpretation which is quite fallacious. It does not in the least imply any change in acid-base balance. True, in certain types of acidosis, for example, diabetic coma, the accumulation of ketone acids is directly responsible for the acidosis, but in the vast majority of instances of ketonuria, no change in the acid-base balance is discernible, and it is unlikely that any change is present. The presence of ketone bodies in the urine must only be taken as evidence of incomplete combustion of fat. There is generally found accompanying this a marked increase of protein catabolism, which may further increase ketone production since a portion of the protein molecule forms ketones. The incomplete combustion of fat is associated in all cases with an
absolute or relative diminution in the combustion of carbohydrate either because of the body’s inability to deal with it, as in diabetes, or because carbohydrate is not available as in starvation. It is probable that it is not so much the combustion of carbohydrate as the amount of glycogen in the liver, which prevents ketone-production, and it is held by some that this regulating effect controls the synthesis as well as the oxidation of the ketones.

Incidence of Ketonuria.—Howland and Marriott have likened the occurrence of ketonuria to that of fever, remarking that it occurs in most of the infections in childhood with about the same frequency as fever. Indeed, one could go further and suggest that in many instances the fever is the determining factor in the production of the ketonuria.

Statistics vary considerably regarding the incidence of ketonuria in children, the percentages found by American observers being consistently lower than those reported in Britain. Holt, for example, gives an incidence of 30 per cent. in 200 consecutive cases on admission to hospital. Of 300 cases examined on admission to the Royal Hospital for Sick Children, Glasgow, there were 54.7 per cent. who showed ketonuria as evidenced by a positive Rothera test (Table XI). Frew, in London, found 61.2 per cent. in over 600 children.

Fever, anorexia, or the relative starvation to which patients are so commonly subjected on admission to the ward all act as aetiological factors in producing an incomplete combustion of fat. Mental excitement is probably another factor, and may be of greater importance than is generally believed. The reasons for suggesting this are two. Firstly, fever and
anorexia developing in subjects already resident in the ward and accustomed to hospital environment often occur without acetonuria. Secondly, twenty-four hours’ starvation in an afebrile child does not necessarily produce ketonuria. The immediate cause of the ketonuria, of course, is the lack of available glucose for combustion. This type of ketonuria can be prevented or made to disappear, if present, by the liberal use of carbohydrate in the form of cane-sugar or glucose.

**KETOSIS AND KETGENIC DIET IN THE TREATMENT OF EPILEPSY**

Within comparatively recent years the production of a ketosis has been used in the treatment of certain diseases, most prominently epilepsy. The results obtained on the whole have been encouraging enough to stimulate much investigation.

Some fifteen years ago, Danish workers pointed out...
that the relationship between the ammonia nitrogen, total nitrogen, and pH of the urine in epileptic patients is much more irregular than in the healthy individual. This conclusion has been contested, and it is now the general opinion that this "dysregulatio ammoniaci" does not always occur in epilepsy and may be found in other conditions. It, however, served the purpose of attracting attention to the possibility of acid-base balance disturbances in epilepsy. In the blood there is little evidence to be found of any abnormal acid-base equilibrium. Although it has been claimed that there is a tendency to alkalosis just prior to an epileptic seizure, the results of most workers do not support this. The bicarbonate content, while probably showing in epilepsy greater variations than in health, is practically always found within normal limits. It is known, however, that over-ventilation, short periods of anoxæmia and administration of alkali, all procedures tending to cause alkalosis, are often able to precipitate seizures. Conversely, the adoption of measures leading to the production of an acidosis has an inhibitory action on the attacks. Thus the administration of carbon dioxide, the ingestion of acid-producing salts (CaCl₂, NH₄Cl), or ketogenic diets, have all been used with some success in reducing the number of seizures.

It is clear, then, that while an actual change in the acid-base equilibrium does not necessarily occur, there is in idiopathic epilepsy a state of affairs which is readily influenced by changes in this equilibrium. The administration of a ketogenic diet has been the most generally adopted measure to obtain the alterations in the acid-base balance. The actual constituents of such a diet can be obtained from several of the modern books dealing with epilepsy. (See Appendix I.) Briefly,
the therapy consists in putting the subject on a high-fat, low-carbohydrate diet comprising one and a half parts of ketogenic substance to one part of anti-ketogenic substance, this proportion being increased to three or even four according to the requirements in the individual case. In actual practice, the following simple equation enables one to work out a diet with a minimum of trouble.

\[
\frac{\text{Ketogenic substance}}{\text{Anti-ketogenic substance}} = \frac{\text{Fat, gm.} + \frac{1}{4} \text{Protein, gm.}}{\text{Carbohydrate, gm.} + \frac{1}{4} \text{Protein, gm.}}
\]

Recent work, however, has shown that the beneficial effects of such a diet are not entirely dependent either on the degree of ketonuria produced or on the production of an actual change in the reaction of the blood, in spite of the fact that the beneficial action of the diet in epilepsy seems to be neutralised by the addition of alkali.

It will be more profitable first to consider the changes produced by ketogenic diet in the blood and urine and on the metabolic processes generally, and thereafter to discuss in what manner the therapeutic effect takes place.

**Blood.**—The administration of a ketogenic diet causes a rapid increase in the acetone bodies in the blood, often within twenty-four hours of the commencement of the diet. After about seven days, the ketonaemia tends to diminish although the diet is continued as before (Figure XVI). This suggests that the metabolism is able to adjust itself partially at any rate to the new conditions. An invariable accompaniment of the ketonaemia produced by ketogenic diet is a fall in the carbon dioxide content of the blood (Figure XVI).
The fasting blood sugar is often reduced considerably, but a more striking effect of the intermediate carbohydrate metabolism is the high rise and delayed fall in the blood sugar curve following the ingestion of glucose (Figure XVII). Theoretically, one might expect that the opposite would occur since a liver relatively empty of glycogen should, after the ingestion of glucose, be able to store large amounts without permitting excess to escape into the circulation. Actually, the existing ketosis seems to impair the glycogenic function to such an extent that a high rise and delayed fall of the blood sugar occur. The low
fasting level in subjects with ketosis, presumably results from the increased call for sugar by the tissues and the depleted stores of glycogen available.

**Figure XVII**

**SHOWING EFFECT OF KETOGENIC DIET ON THE BLOOD-SUGAR CURVE AFTER INGESTION OF GLUCOSE (1 GM. PER KG. BODY WEIGHT).**

(From Gilchrist, *Arch. Dis. Child.*, 1932, vii, 172.)

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**Urine.**—Ketonuria is the most prominent finding, the increase of ketones in the urine running more or less parallel with the degree of ketonæmia (Figure XVI). The urine becomes strongly acid in reaction, the volume and the output of fixed base are increased, and the ammonia excretion is raised together with the ammonia coefficient (Figure XVIII). Of the fixed base
the bulk of the increased excretion is made up of sodium. Although the urinary output of calcium may be trebled, the normal excretion of this substance by

**Figure XVIII**

**Showing effect of ketogenic diet and ingestion of hydrochloric acid on ammonia coefficient of urine.**

the urine is so small that the extra calcium lost may not amount to more than 0.2 gm. per day.

**Metabolic Disturbances.**—During the period of ketogenic diet there occurs a diminished retention of calcium, phosphorus, chlorine, and sodium, and often
a loss of weight in the subject. This loss in weight is almost entirely due to a withdrawal of tissue fluid. The whole series of events may be attributed to the excessive production of acids (the ketone bodies).

The Mode of Action of the Ketogenic Diet in Epilepsy.
—The chief effects of the administration of a ketogenic diet may be summarised as follows:

1. Production of a ketosis.
2. Production of an acidosis.
3. Extensive loss of fluid.

It has been suggested that over-production of acetone bodies, acting as a sedative on the central nervous system, is the cause of the improvement following relative carbohydrate starvation. It has, however, been clearly demonstrated that while the addition of an alkali diminishes the beneficial effect of the ketogenic diet, it does not lessen and may even increase the over-production of ketones. From this it is clear that it is not the action of ketones *per se* that is responsible for the amelioration. Nor can the upset in the carbohydrate metabolism itself be responsible for the reduced number of seizures, since abnormal carbohydrate metabolism still exists on the alkali-ketogenic régime.

It would appear, therefore, that it is the presence of the acidosis which exerts the favourable action. There seems to be a rough relationship between the number of attacks and the carbon dioxide content of the blood. Furthermore, an acidosis brought about by acid-producing salts may without the production of acetonaemia lead to improvement. On the other hand, it
has been common experience that improvement following acidosis, especially that produced by inorganic salts, is only temporary, although the carbon dioxide content of the blood may remain low. Moreover, the production of an alkalosis does not necessarily increase the number of seizures.

The most recent work has shown that there exists a "superficial relationship between water balance and the occurrence of epileptic seizures." There appears to be a tendency for the epileptic subject to retain water in amounts which become harmful, thus precipitating the active phase of the disease. Convulsions tend to occur when a positive water balance above a certain magnitude is established. When diuresis occurs following a seizure, it temporarily favours the prevention of further attacks. Whether this effect of the extra water is due to mechanical processes (increasing pressure on nerve cells), or to disturbance in cell-metabolism by excessive hydration, has not yet been determined. As has already been stressed, one of the effects of acidosis is to produce a diminished retention of water, and it is difficult to assess the relative importance of the acidosis *per se* and its dehydrating effect in causing a diminution in the number of seizures. Certainly, any anti-diuretic measures such as the administration of an extract of the posterior lobe of the pituitary seem to increase the number of attacks. Likewise, sudden increase in the amount of water ingested is said to have an aggravating effect. It would seem, therefore, that in the treatment of epilepsy, ketogenic diet or any other method of inducing acidosis depends for its beneficial action on the dehydrating effect produced. This view is supported by the finding that water storage occurs
between the attacks and that an attack is followed by a release of the fluid.

Recently, Bridge and Iob have pointed out that the removal of sodium may also play a part in the prevention of seizures. They found that if ketogenic diet was not successful in removing surplus sodium even in the presence of acidosis and ketonæmia, fasting might bring about sodium loss and consequent improvement.

Whether loss of sodium or loss of water is the more potent factor is, in a sense, of little import from the practical point of view since most dehydrating measures entail the reduction of the sodium content of the tissue-fluids.

**KETONIC DIET IN THE TREATMENT OF PYURIA**

Within the last two years ketogenic diet has been used in the treatment of pyogenic infections of the urinary tract. Our experience of this is not as yet sufficient to enable us to express any opinion but very promising results have been reported by several workers. Helmholz, who originally suggested this form of treatment, states that the urine of a patient on a ketogenic diet becomes bactericidal at a pH of 5.6 or lower. Apparently it is not the extreme degree of acidity of the urine *per se* which exerts the beneficial action, since urines made acid to the same degree by means of such salts as ammonium chloride do not show the same properties. Neither does it appear to be the mere presence of ketone bodies in the urine, although the state of ketosis is required. The production of a highly acid urine, together with a ketonuria, is essential in order to obtain a bactericidal effect.
CHAPTER XII

SALICYLATE POISONING

The beneficial effect of sodium salicylate in the treatment of acute rheumatic arthritis is approximately proportionate to the amount of the drug given. Failure to obtain good results is due to the smallness of the dose. When large doses are used, particularly if unaccompanied by alkali, signs and symptoms of salicylate poisoning are not infrequently observed. In some children, indeed, there seems to be a special idiosyncrasy to the drug so that even small doses may produce symptoms of intolerance. A recognition of these signs is of importance, as the condition when it appears, tends to develop rapidly, and most alarming symptoms arise unless adequate preventive or curative measures are taken.

It may be stated at once that the clinical and biochemical evidence indicates clearly that the signs and symptoms of poisoning by salicylate are due in part at any rate to the development of a non-gaseous acidosis. Although there are several facts which go to show that acidosis is not the sole cause of the manifestations, the severity of the acidosis can nevertheless be taken as an indication of the severity of the poisoning. Furthermore, as we shall discuss later, this salicylate acidosis is not a mere acid-poisoning one such as occurs from the use of an acid-producing
SALICYLATE POISONING

salt, e.g. calcium chloride, but depends for its production on damage certainly to kidney and probably also to liver.

**Clinical Manifestations.**—Vomiting is a constant and early sign, and precedes all other manifestations of salicylism. Drowsiness and confused mental states or mental torpor occur in some instances. Many patients become apathetic and disinterested in their surroundings, and in one instance we have observed a thick and slurring speech. It is very doubtful if these signs are attributable to acidosis per se. Air-hunger of greater or less severity, but not necessarily in proportion to the other signs, occurs in all patients; sometimes it is extreme. This is the typical acyanotic dyspnœa which is associated with all forms of non-gaseous acidosis. Tinnitus is not common in children, and when it does occur, is not necessarily associated with the presence of acidosis.

**Biochemical Findings.**—The total carbon dioxide content of the blood is markedly lowered. We have found that when the figure fell below 40 volumes per cent., symptoms such as vomiting and slight air-hunger made their appearance. When the carbon dioxide fell to 80 volumes per cent., symptoms were invariably present and frequently severe. The chlorine and fixed base of the blood are not as a rule altered, nor is the non-protein nitrogen raised.

Ketonuria may or may not be present; this depends on the nutritional state of the patient. A full carbohydrate intake which will ensure an ample store of glycogen, will prevent the appearance of ketone bodies in the urine. Usually, however, rheumatic children are on a reduced diet, especially in the early stages of treatment, and in them a well-marked ketonuria is the rule.
Albuminuria occasionally appears during salicylate administration. This naturally leads to the assumption that salicylate damages the renal cells. Such, we believe, is actually the case, and this is supported by the observation that there is impairment of renal function in patients suffering from salicylism. For example, the urea concentrating power is considerably diminished (Table XV), as is also the ammonia output (Table XII). Actually, in salicylate poisoning we have noted a consistent fall in the ammonia coefficient, although the opposite might be expected in a pure acid-poisoning type of acidosis. The explanation probably lies in kidney damage, but it must be remembered that this defence of increased ammonia production, even in other forms of non-gaseous acidosis, is usually late in coming into action (see Chapter V). The excretion of nitrogen is also diminished.

**Table XII**

**SHOWING CHANGES OBSERVED IN THE URINE AS A RESULT OF ADMINISTRATION OF SODIUM SALICYLATE.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Period (6 days each)</th>
<th>Titratable Acidity in c.c. N/10 per day</th>
<th>Ammonia in gm. per day</th>
<th>Total Nitrogen in gm. per day</th>
<th>Ammonia Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.</td>
<td>I</td>
<td>167.2</td>
<td>0.378</td>
<td>9.31</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>255.3</td>
<td>0.311</td>
<td>8.22</td>
<td>3.8</td>
</tr>
<tr>
<td>M.</td>
<td>I</td>
<td>155.2</td>
<td>0.291</td>
<td>8.49</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>222.3</td>
<td>0.231</td>
<td>7.68</td>
<td>3.0</td>
</tr>
<tr>
<td>S.</td>
<td>I</td>
<td>132.5</td>
<td>0.344</td>
<td>7.92</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>176.9</td>
<td>0.189</td>
<td>7.41</td>
<td>2.70</td>
</tr>
</tbody>
</table>

During Period II sodium salicylate (10–15 grains four-hourly) was given. The diets were identical in both periods. The figures show average daily excretion.
(Table XII), an observation not without significance in explaining the aetiology of the acidosis.

**THE ACTION OF ALKALI**

The beneficial action of alkali in salicylate adminis-

**Table XIII**

**SHOWING TOLERANCE OF CHILDREN TO SODIUM SALICYLATE WITHOUT SODIUM BICARBONATE.**

<table>
<thead>
<tr>
<th>Name.</th>
<th>Age in Years</th>
<th>Daily dose of Sod. Sal. (grains)</th>
<th>Duration of Treatment (days)</th>
<th>Vomiting.</th>
<th>Other signs of intolerance.</th>
<th>Acetonuria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.G.</td>
<td>7</td>
<td>50</td>
<td>40</td>
<td>nil.</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>M.N.</td>
<td>12</td>
<td>50</td>
<td>23</td>
<td>nil.</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>F.K.</td>
<td>10</td>
<td>60</td>
<td>35</td>
<td>1</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>L.J.</td>
<td>12</td>
<td>60</td>
<td>14</td>
<td>1</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>J.McL.</td>
<td>9</td>
<td>60</td>
<td>48</td>
<td>nil.</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>J.W.</td>
<td>8</td>
<td>60</td>
<td>30</td>
<td>4</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>K.C.</td>
<td>9</td>
<td>60</td>
<td>16</td>
<td>5</td>
<td>nil.</td>
<td>nil.</td>
</tr>
<tr>
<td>A.S.</td>
<td>6</td>
<td>90</td>
<td>3</td>
<td>nil.</td>
<td>Tremor, nervousness, acidosis.</td>
<td>nil.</td>
</tr>
<tr>
<td>J.S.</td>
<td>7</td>
<td>90</td>
<td>4</td>
<td>2</td>
<td>Nervousness, headache, depression.</td>
<td>+ last day.</td>
</tr>
<tr>
<td>W.P.</td>
<td>7</td>
<td>90</td>
<td>2</td>
<td>2</td>
<td>Tremor, nervousness, headache.</td>
<td>nil.</td>
</tr>
</tbody>
</table>

*This patient vomited twice before commencement of sodium salicylate administration.*

administration has been known for many years, but comparatively little investigation has been carried out regarding its mode of operation. Generally speaking, and irrespective of age, sixty grains of salicylate of sodium per day (ten grains four-hourly), is the maximum amount which, without the addition of alkali, can be tolerated by a child without the appearance of toxic signs. In a series of cases we found that
fifty grains never produced any ill-effects but sixty grains occasionally produced vomiting. When the daily amount was increased to ninety grains, signs of intolerance invariably appeared in from three to four days (Table XIII). With the addition of sufficient alkali (twice as much alkali as salicylate), ninety or

**TABLE XIV**

**SHOWING BENEFICIAL INFLUENCE OF PREVIOUS ADMINISTRATION OF SODIUM BICARBONATE ON TOLERANCE OF CHILDREN TO SODIUM SALICYLATE.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Age: Years</th>
<th>Duration of administration of Sod. Sal. gr. 90 + Sod. Bic. gr. 180 Days</th>
<th>Vomiting</th>
<th>Duration of administration of Sod. Sal. gr. 90 Days</th>
<th>Vomiting</th>
<th>Other signs of intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.McG.</td>
<td>11</td>
<td>80</td>
<td>nil</td>
<td>28</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>J.W.</td>
<td>9</td>
<td>78</td>
<td>nil</td>
<td>18</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>M.J.</td>
<td>11</td>
<td>68</td>
<td>nil</td>
<td>33</td>
<td>nil</td>
<td>One on 6th day</td>
</tr>
<tr>
<td>M.F.</td>
<td>9</td>
<td>67</td>
<td>nil</td>
<td>20</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>M.J.</td>
<td>8</td>
<td>34</td>
<td>nil</td>
<td>11</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>R.Mci.</td>
<td>9</td>
<td>28</td>
<td>nil</td>
<td>12</td>
<td>nil</td>
<td>One on 2nd day</td>
</tr>
<tr>
<td>D.W.</td>
<td>8</td>
<td>27</td>
<td>nil</td>
<td>15</td>
<td>nil</td>
<td>One on 8th day</td>
</tr>
<tr>
<td>R.S.</td>
<td>8</td>
<td>24</td>
<td>nil</td>
<td>23</td>
<td>nil</td>
<td>Twice</td>
</tr>
<tr>
<td>A.McC.</td>
<td>11</td>
<td>7</td>
<td>nil</td>
<td>6</td>
<td>Twice on 5th day. Twice on 6th day.</td>
<td>Headache, depression.</td>
</tr>
</tbody>
</table>

even one hundred and twenty grains daily may be given with perfect safety, provided that due attention is paid to the condition of the bowels and constipation avoided. It is an interesting observation that in those patients who had a course of salicylate combined with alkali, the signs of poisoning on omitting the alkali, were much less prone to develop (Table XIV).
Two most important deviations from normal are prevented by the addition of the alkali. Firstly, the fall in the total carbon dioxide content of the blood, which incidentally is a good guide to the severity of the acidosis, is prevented, or if the fall has occurred, the alkali is rapidly effective in restoring it to normal (Figure XIX). Secondly, the poor urea-concentrating power of the kidney which is brought about by

**TABLE XV**

**SHOWING EFFECT OF ADMINISTRATION OF SODIUM SALICYLATE WITH AND WITHOUT SODIUM BICARBONATE ON UREA-CONCENTRATING POWERS OF KIDNEY.**

<table>
<thead>
<tr>
<th>Name</th>
<th>B.</th>
<th>M.</th>
<th>S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period I.</td>
<td>II.</td>
<td>I.</td>
<td>II.</td>
</tr>
<tr>
<td>Per cent. of urinary urea before administration of urea</td>
<td>1.56</td>
<td>1.08</td>
<td>1.86</td>
</tr>
<tr>
<td>Per cent. of urinary urea in 1st hour after administration of urea (15 gm.)</td>
<td>1.74</td>
<td>1.74</td>
<td>1.44</td>
</tr>
<tr>
<td>Per cent. of urinary urea in 2nd hour after administration of urea (15 gm.)</td>
<td>1.44</td>
<td>2.86</td>
<td>1.22</td>
</tr>
</tbody>
</table>

*Period I.—Sodium salicylate alone.*  
*Period II.—Sodium salicylate combined with twice the amount of sodium bicarbonate.*

salicylate can be prevented, or if present, can be restored to normal by the alkali (Table XV).

In searching for a reason why the alkali is so beneficial in preventing and putting away signs of salicylate poisoning, the beneficial effect on kidney function seems to be an important factor, but its influence on the rate of excretion of the salicylate by the kidney must also be taken into consideration. Observations on this point have shown that the alkali causes a marked increase in the salicylate content of
the blood, and at the same time the amount excreted in the urine is increased two-, three-, or even fourfold (Table XVI). The fate of the salicylate not excreted, particularly when alkali is not given, is still unknown. It is conceivable that it is fixed in the tissues in some way, and thus is not permitted to exert its beneficial action.

**Table XVI**

**INFLUENCE OF SODIUM BICARBONATE ON THE URINARY EXCRETION AND BLOOD-CONTENT OF SODIUM SALICYLATE.**

<table>
<thead>
<tr>
<th>Name</th>
<th>B.</th>
<th>M.</th>
<th>S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period</td>
<td>I. 6 days</td>
<td>II. 6 days</td>
<td>I. 7 days</td>
</tr>
<tr>
<td>Total amount of sod. sal. given (gm.)</td>
<td>23.33</td>
<td>23.33</td>
<td>34.90</td>
</tr>
<tr>
<td>Total amount of sod. bic. given (gm.)</td>
<td>—</td>
<td>46.66</td>
<td>—</td>
</tr>
<tr>
<td>Total amount of sod. sal. excreted (gm.)</td>
<td>6.069</td>
<td>20.25</td>
<td>21.33</td>
</tr>
<tr>
<td>Per cent. of sod. sal. excreted</td>
<td>26.0</td>
<td>86.8</td>
<td>91.4</td>
</tr>
<tr>
<td>Salicylate content of blood (mgm. per 100 c.c.)</td>
<td>9.3</td>
<td>29.0</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Period I.—Salicylate alone.  
Period II.—Salicylate with the addition of alkali.

It seems impossible to avoid the conclusion that one factor in the prevention of salicylate poisoning by alkali is the increased rate of excretion. This is perhaps in part due to the increased head of salicylate in the blood, but the evidence is conclusive that kidney damage is also prevented by the alkali. The higher content of salicylate in the blood probably has a more powerful therapeutic action.
EFFECT OF GLUCOSE ADMINISTRATION ON SALICYLATE POISONING

It has been suggested by Hanzlik that the acidotic states occurring in salicylate poisoning and diabetic coma have a common cause, presumably, the overproduction of ketone bodies (ketosis). It is true that ketonuria frequently does occur in children suffering from salicylate poisoning, but this is dependent, as we have already stated, on the diminished glycogen stores in the liver. The mere fact that salicylism can and frequently does occur without ketosis is sufficient proof of the fallacy of such a theory. Further information can be obtained, however, by observing the effect of glucose in the prevention or cure of the acidosis. The previous administration of glucose does not prevent either the development of symptoms or the

FIGURE XIX

EFFECT OF GLUCOSE AND SODIUM BICARBONATE IN PREVENTION OF FALL IN CARBON DIOXIDE CONTENT OF BLOOD IN SALICYLATE POISONING.
fall in the carbon dioxide content, nor can these be corrected by glucose (Figure XIX). It is obvious, therefore, that ketosis has no ætiological significance in the acidosis of salicylate poisoning.

The fasting blood sugar is generally raised by about 15 per cent. during the period of salicylate ingestion, whereas in ketosis produced by ketogenic diet the fasting blood sugar is lower, and in diabetic ketosis much higher than normal. In salicylate poisoning there is obviously in the blood stream a sufficiency of glucose. It is possible that the action of the salicylate on the tissues inhibits the utilisation of the sugar, but a much more probable explanation is that the salicylate exerts a toxic action on the liver cells which are thus rendered less capable of storing glycogen.

THE CAUSE OF THE ACIDOSIS IN SALICYLATE POISONING

From a consideration of the clinical and chemical findings, there would appear to be little doubt that in salicylism there is a marked disturbance in acid-base equilibrium. The clinical picture of acyanotic dyspnoea, the fall in the carbon dioxide content of the blood, and the favourable response to alkali, all point convincingly to the presence of a non-gaseous acidosis.

Theoretically, the excess acid may be either salicylic acid or acids produced as a result of disordered catabolism. The amount of salicylic acid is quite insufficient to account for the carbon dioxide deficit. In one instance, for example, we found a salicylic acid content of 13 mgm. per 100 c.c. (0.00094 mol. per litre), which would account for a diminution in the carbon dioxide of only 2 volumes per cent., whereas
the actual fall was more than 20 volumes per cent. It is clear, therefore, that the fall in carbon dioxide is not merely the result of its replacement by salicylic acid.

It is possible that the toxic action of salicylate on the liver is responsible for abnormal protein breakdown, with the resultant production of acid nitrogenous substances. Furthermore, renal function is impaired, and the ammonia output reduced, so that urinary excretion of acids is below normal. It would appear, therefore, that the increased production of acid substances combined with defective excretion offers a satisfactory explanation for the excess acid accumulation which leads to the fall in the carbon dioxide content of the blood and the symptoms and signs of a non-gaseous acidosis.

**THERAPEUTIC ASPECTS**

The biochemical findings show quite definitely the value of alkali during salicylate administration, and are in complete agreement with the clinical evidence. So conclusive is this evidence that it is unjustifiable to give large doses of salicylate unless combined with alkali. Sodium bicarbonate is probably the alkali of choice, and should be given in amounts equal to twice that of the salicylate. This permits a greater concentration in the blood, accelerates the excretion of the salicylate and, as we have shown, protects the functional activities of the kidney and probably also of the liver and other organs.

If signs of salicylate poisoning are present, the salicylate should, of course, be discontinued, but the indications are for even greater dosage of the alkali.
Glucose either as a preventive or curative agent is, as we have shown, useless. If ketonuria be present, however, it is wise to give some glucose as it will have a beneficial effect in restoring the fat metabolism to normal although not necessarily improving the acidosis. If the urine is free of ketone bodies, there is no apparent advantage in giving glucose.
CHAPTER XIII

ACIDOSIS ASSOCIATED WITH ANÆSTHESIA

The disturbances of acid-base equilibrium associated with the administration of anaesthetics fall into two main groups: (1) those changes occurring during anaesthesia, and (2) those following anaesthesia. Of these, the former are relatively unimportant, but the latter are always serious, and not infrequently result in the death of the patient.

ANAESTHESIA

The emotional excitement so frequently encountered before operation may have a great influence on carbohydrate metabolism. As a result either of impulses directly from the nervous system or of stimulation of the adrenals, there occurs relative hepatic insufficiency with consequent hyperglycaemia and ketosis. This may lead to a lowering of the carbon dioxide content of the blood, but a change of this nature is usually transient.

Early in anaesthesia, and continuing throughout, the total carbon dioxide content of the blood falls. This, at first, was attributed to over-ventilation with "washing out" of carbon dioxide and resulting gaseous alkalosis. More recently, Cullen and his co-workers have shown that there is an actual fall in the pH of the blood, so that the condition must be a non-gaseous acidosis. The acidosis does not occur only
in inhalation narcosis, but has been reported with both local and spinal anaesthesia. Ketosis frequently occurs after the fall in carbon dioxide content of the blood and, although it is in chloroform anaesthesia that it is most usually seen, it has also been found in all types of anaesthesia.

There are many explanations of the cause of the acidosis. Anoxæmia and muscular activity during the induction of narcosis have been suggested as causes of accumulation of acids in the tissues and blood. In normal circumstances the contraction of muscle leads to the production of lactic acid and some of this is completely oxidised to water and carbon dioxide, but about eighty per cent. is resynthesised to glucose and glycogen. This resynthesis can only occur when there is an ample supply of oxygen. It is thus possible that the slight rise in the lactic acid content of the blood occurring during general anaesthesia may be explained by lack of oxygen. Uric acid and inorganic phosphate are increased slightly, but not rapidly enough to account for the fall in the carbon dioxide. Long attributes the acidosis to disturbance of carbohydrate metabolism. Certainly the blood sugar rises slightly during light anaesthesia; this is probably due to increased glycogen breakdown. The ketosis is unlikely to be responsible since it is said to appear only after the fall in carbon dioxide. Anaesthetic acidosis, however, is seldom serious, and with cessation of anaesthesia the equilibrium rapidly returns to normal. The fact that it does occur indicates that in general anaesthesia enrichment of the inspired air with oxygen is of advantage, since in the presence of ample oxygen the metabolic processes are more likely to be carried on to completion.
Surgical shock may lead to the production or aggravation of a non-gaseous acidosis. In shock there is a failure of circulation leading to defective oxidation and excretion and consequent accumulation of acid substances with resulting diminution of the carbon dioxide content of the blood. Where there has been great loss of blood, the deficiency of haemoglobin tends to aggravate the condition, because of the impaired supply of oxygen to the tissues.

**POST-OPERATIVE ACIDOSIS**

Post-operative acidosis is a term frequently used in medical literature, and includes the condition known as delayed chloroform poisoning. Fortunately its incidence is rare: when it occurs it is of the utmost gravity, and a fatal issue only too frequently ensues. Uncontrollable vomiting usually sets in about twenty-four hours after operation, and is associated with marked dyspnoea. The pulse becomes frequent and weak, and the face sunken. The whole picture presented is one of an extremely ill acidotic patient.

The total carbon dioxide content of the blood falls rapidly and there is a marked ketonuria. If carbohydrate has been given prior to operation and continued, the blood sugar is well above normal, and glycosuria is commonly present. If carbohydrate has been withheld, it is said that the blood sugar is low.

We are indebted to Dr. Leonard Findlay for permission to publish the following case from his reports.

*Case II.—A. F., male, aged thirteen months. Previously healthy. Admitted to hospital on 6.3.30 with a right-sided irreducible inguinal hernia and hydrocele of the cord. During the previous 24 hours he had vomited twice.*

*On admission temperature 99°, pulse 120, and respirations 24. Operation for radical cure was performed the same day;*
anæsthesia induced with chloroform and continued with ether. On 7.3.30 patient seemed well. Temperature 99°F., pulse 128, respirations 32. He was receiving the routine treatment of glucose and saline *per rectum* and glucose *per os*.

On 8.3.30 child was pale and listless. The respirations were markedly sighing in character. The breath smelled of acetone. There had been no vomiting and the child was not jaundiced.

Seen by Dr. Leonard Findlay at 10 a.m. The following is an extract from his note on that occasion: "Child presents typical picture of acidosis—tossing about in bed with deep, frequent and sighing respiration. Child flushed although temperature normal. Breath smells of acetone—in fact, one smelt acetone on entering the ward. Urine, which is acid, contains only a trace of acetone but reduces Fehling’s solution. Physical examination negative."

**Blood**, taken at 10.30 a.m.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total carbon dioxide</td>
<td>30.5%</td>
<td></td>
</tr>
<tr>
<td>Sugar</td>
<td>331.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Chlorine</td>
<td>370.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Non-protein nitrogen</td>
<td>85.6 mgm.</td>
<td>per cent.</td>
</tr>
</tbody>
</table>

Insulin and glucose were given together with sodium bicarbonate (twenty grains every three hours). At 5.15 p.m. the child seemed slightly better. At 7.15 p.m. the urine contained only a trace of glucose and acetone. At 8.30 p.m. blood analysis gave the following results:

<p>| | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total carbon dioxide</td>
<td>52.4%</td>
<td></td>
</tr>
<tr>
<td>Sugar</td>
<td>164.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Chlorine</td>
<td>360.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Non-protein nitrogen</td>
<td>39.3 mgm.</td>
<td>per cent.</td>
</tr>
</tbody>
</table>

At 11.35 p.m. the urine was free of sugar but contained rather more acetone than before.

On 9.3.30 at 5.15 a.m. there was no glucose or acetone in the urine. At noon the temperature was 105.4°F. (it had been steadily rising since 4 p.m. on the previous day). Child flushed with rapid breathing. During examination child took a short but definite generalised convulsion.

**Blood**, taken at 10 a.m.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total carbon dioxide</td>
<td>75.1%</td>
<td></td>
</tr>
<tr>
<td>Sugar</td>
<td>299.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Chlorine</td>
<td>365.0 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Non-protein nitrogen</td>
<td>146.7 mgm.</td>
<td>per cent.</td>
</tr>
<tr>
<td>Van den Bergh (direct and indirect)</td>
<td></td>
<td>negative.</td>
</tr>
</tbody>
</table>
The urine contained neither acetone nor glucose: its urea content was 2.16 per cent. and sodium chloride 0.1755 per cent. The administration of glucose was continued. Temperature 108.6° F.; child died at 3.30 p.m.

Post-mortem examination by Dr. J. W. S. Blacklock revealed "some cloudy swelling and fatty change in the liver but no evidence of any bile staining, marked fatty change in the kidneys, and a sub-pericranial haemorrhage over the right frontal bone, a few meningeal haemorrhages on the surface of the brain. The thymus and thoracic glands are small."

The findings here indicate clearly: (1) that the metabolism of glucose is definitely abnormal, (2) that the restoration of the blood carbon dioxide content to a high level does not necessarily mean a betterment of the condition, (3) that the disappearance of ketones from the urine is not necessarily associated with improvement, and (4) that the increase in the non-protein nitrogen and chlorine of the blood is not due to inability of the kidneys to concentrate these substances. It is also clear that insulin was effective in reducing the level of the blood sugar.

The aetiology of the condition is obscure, and the picture presented resembles somewhat that seen in acute yellow atrophy of the liver, where also a non-gaseous acidosis has been reported. It is generally held in this country that chloroform is the important factor, and the term delayed chloroform poisoning is the one in common use. German literature, however, contains reference to instances presenting exactly the same features and with fatal results, following open-ether administration. Nevertheless, there is a general feeling that chloroform should be avoided. The severity of the surgical procedures, the nature of the pathogenic process present and the presence of sepsis or loss of blood seem to bear no relationship to the development of post-anæsthetic acidosis. Many believe
that pre-operative starvation is a potent factor. In the experience of most surgeons the administration of a rich carbohydrate diet prior to the anaesthesia is of advantage in preventing post-operative ketosis and vomiting. With this we are in agreement, although in the two patients whom we have seen suffering from post-operative acidosis, carbohydrate had not been withheld prior to the operation. The constant finding post-mortem of extensive fatty infiltration of the liver suggests that the accumulation of acid substances is due to toxic degeneration of the liver. While the acidosis must play a part in injuring the organism, its action is subsidiary to that of the toxic substances produced in the course of the acute hepatic degeneration. As we have said, the restoration to normal of the carbon dioxide content of the blood within twenty-four hours of the onset of symptoms of acidosis does not necessarily lead to recovery.

One other theory is that the metabolic upset is the result of fat emboli in various organs. The blood in post-anæsthetic acidosis certainly contains an excessive amount of lipoid, but apart from this, there seems to be little evidence in favour of this hypothesis.

**Aspects of Treatment.**—So far no test for the detection of susceptibility to post-operative acidosis has been found. Instances have been reported where this complication has been met with a second time in the same patient. In these cases treatment with glucose did not prevent the onset of the condition.

In most surgical clinics the pre-operative régime of purging and fasting has now been discarded. Instead, an ample carbohydrate diet is given on the previous day, and even a few hours before the operation glucose is given. It is difficult to decide what effect
this has had on the incidence of post-operative acidosis, but it seems rational to assume that the patient whose glycogen store is enriched by the liberal administration of glucose is less liable to the minor post-operative discomforts such as nausea. Whether a susceptible individual can be saved from the grave risks of post-operative acidosis by such a régime remains a controversial subject. At any rate, prophylactic treatment of this kind is in keeping with our present knowledge. When the complication actually arises the giving of abundant fluids, glucose and alkali is certainly indicated.
CHAPTER XIV

TETANY

For many years past the disturbance in the acid-base balance in tetany and the part this may play in its ætiology have been subjects of much investigation. Certainly, as far as the efficient treatment of the condition is concerned, consideration of the reaction of the blood is of importance.

At the present time, it is generally believed that a diminution in the serum content of ionised calcium is the immediate cause of the manifestations of tetany. According to this view the total calcium content of the blood may be normal, and yet tetany may exist if the percentage present in the ionised or free form is diminished. This theory, while not universally accepted, generally provides a satisfactory explanation of the various blood changes found in different types of tetany, and gives a common ætiological factor which simplifies an understanding of the condition. There are many conditions widely divergent at the first glance, which may bring about this fall in ionic calcium, and one has only to consider removal of parathyroids and voluntary hyperpnoea to realise the truth of this (Table XVII).

Infantile Tetany.—This is the common type of tetany, and in its active form there is always a fall in both the total and ionic forms of serum calcium. It is associated in the vast majority of cases with active or
healing rickets. Normally the total serum calcium is 10 mgm. per cent. and the ionic fraction is roughly one-third of this. In infantile tetany symptoms, as a rule, become manifest when the total calcium falls to 7 mgm. per cent. or lower. Some authorities uphold the view that in this form there is an alkalosis. Their evidence is based on urinary changes and changes in the alkaline reserve, but it does not appear to be sufficient to warrant such a conclusion. Certainly there is no appreciable change in the pH, and we have not found significant changes in the carbon dioxide content of the blood.

One is impressed, however, by the frequency with which fever will bring on an attack of tetany, or make active a latent form. The convulsions which frequently usher in an acute infection in an infant or a young child are more often than not associated with a low blood calcium, and in such instances, should be looked upon as tetany.

**Table XVII**

**Showing Commoner Changes in Blood Chemistry in Various Types of Tetany.**

<table>
<thead>
<tr>
<th>Type of Tetany</th>
<th>Total Calcium</th>
<th>Inorganic Phosphorus</th>
<th>Total Carbon-dioxide Content</th>
<th>pH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpneic tetany.</td>
<td>Normal or increased.</td>
<td>Diminished.</td>
<td>Increased.</td>
<td>Increased.</td>
</tr>
<tr>
<td>Administration of alkali.</td>
<td>Normal or increased.</td>
<td>Normal or increased.</td>
<td>Increased.</td>
<td>Increased.</td>
</tr>
</tbody>
</table>

**TABLE**

**XVII**

**SHOWING COMMONER CHANGES IN BLOOD CHEMISTRY IN VARIOUS TYPES OF TETANY.**
ACIDOSIS AND ALKALOSIS

Case III.—S.W., female, aged seven months: admitted to ward on 26th October 1930 with the following story:

Healthy at birth: entirely breast-fed, and well until 3 a.m. on morning of admission, when she wakened up and vomited. Vomiting persisted and at 9 a.m. she had a convulsion. Brought to hospital at 10 a.m., temperature 100.2° F. The only disease discovered was a right-sided otitis media. No more fits occurred but two days later laryngismus was heard, Trousseau’s sign was positive and Chvostek’s sign was well marked.

A raised temperature *per se* induces an alkalosis, and it is a plausible argument that the alkalosis so produced is responsible for the fall in the ionised calcium content of the blood, and the appearance of signs of tetany. We would refer again to the extreme difficulty in very young subjects of assessing the changes in acid-base balance disturbances, and this question we feel is one which must still remain *sub judice*.

Tetany Associated with Removal of Parathyroid Glands.—This form of tetany is usually the result of a surgical accident, and occurs when the parathyroid glands are removed in thyroidectomy, the resultant loss of the normal parathyroid secretion being in this case the primary cause. Parathyroidectomy both in man and in animals produces a fall in the blood calcium content. The consensus of opinion is that there is no disturbance of the acid-base balance in this condition, and we shall not discuss it further except to say that it reacts to the acid-therapy in a manner similar to infantile tetany. Paton and Findlay have suggested that guanidine, a toxic substance resulting from protein breakdown, plays an important part in the etiology of this condition.

The Injection of Alkaline Phosphate.—In experimental work, Binger noted that following the injection
of alkaline phosphate (Na$_2$HPO$_4$) in dogs, tetany was induced, but the injection of the acid salt (NaH$_2$PO$_4$) failed to bring this about. The calcium content was lowered in each instance, and presumably the deciding factor in the production of tetany in these experiments was the alkaline nature of the injected salt. Indeed, the acid ammonium phosphate salt ((NH$_4$)H$_2$PO$_4$) not only does not cause the appearance of signs of tetany, but actually by virtue of its acid-producing properties has been used successfully in treating the condition.

**Gastric Tetany.**—True gastric tetany in children is a rare occurrence. Indeed, it is not common at any age. Kussmaul first described the condition in association with dilatation of the stomach, and Osler remarked that it was more likely to occur in those patients who were having gastric lavage, a significant observation in the light of recent facts.

In all cases, the stomach is dilated and there is copious vomiting. The dilatation in infants is usually secondary to congenital pyloric stenosis and in adults to obstruction caused by pyloric ulcer or carcinoma. The sequence of events leading up to the production of gastric tetany is exactly similar to that described under pyloric stenosis (Chapter XV). The vomiting or the gastric lavage causes a loss of chlorine which is reflected in the diminished blood chlorine. This diminution of blood chlorine is made good by a rise in the carbon dioxide content of the blood to neutralise the base left without acid radicles. The resultant rise in bicarbonate leads to the production of a well-marked non-gaseous alkalosis. It is presumably this alkalosis which lowers the ionised calcium of the blood and thus causes the tetany. The following
report of a case of tetany developing in a patient with severe vomiting is illustrative.

Case IV.—G. S., aged sixteen years. Post-mature infant; birth weight 9 lbs.; unduly quiet for first week, “slept all the time.” At three months, a febrile illness with repeated convulsions. When eight years old, “delayed chloroform poisoning” following an anaesthetic for removal of tonsils. Since then, periodic attacks of vomiting resembling cyclical vomiting. Acetonuria was present and the treatment had usually consisted of the administration of glucose and alkali. During an attack, copious water was taken and immediately vomited. Rectal fluids were frequently administered. The respirations fell to 12–14 per minute at the height of the attack.

For the past five years (i.e., after the attacks had been occurring for three years) tetany has appeared when the vomiting has persisted for two or three days (carpo-pedal spasm and occasionally some laryngeal spasm; Chvostek’s sign ++ +). On recovery, which invariably sets in suddenly, the child becomes ravenous for sodium chloride and will put as much as two teaspoonfuls of table salt in a cupful of soup and drink it eagerly.

The blood chemistry at the height of an attack was as follows:

Total carbon dioxide . . . . 82.5 volumes per cent.
Chlorides . . . . . . 230.0 mgm. per cent.
Non-protein nitrogen . . . . . 38.0 mgm. per cent.

The urine remained acid during each attack, which observation suggests some renal factor. The stomach was considerably dilated but no obstruction was present. The drinking and vomiting of large quantities of water resulted in a great loss of chlorine from the tissues and blood, and the condition of the patient was alleviated but not cured by taking saline.

The total calcium content of the blood may be normal or slightly increased, and it has been suggested that this increase in calcium is a protective mechanism on the part of the body to prevent the onset of tetany, calcium having a sedative action. This is not necessarily so, because it has been shown that it is not the total calcium but the ionic fraction which is the factor determining the onset of tetany. This, under the
conditions of extreme degrees of alkalosis, is presumably diminished, since calcium salts are less ionised the greater the alkalinity of the solution.

Of all the cases which suffer from some degree of pyloric obstruction with dilatation of the stomach, only a very few develop tetany. Why this is so is not clear. It does not seem necessarily dependent on the degree of alkalosis per se, since in congenital pyloric stenosis we have frequently observed extreme degrees of non-gaseous alkalosis without any signs of tetany. Neither is it the patient with the greatest diminution in the blood chlorides who is most likely to show signs of tetany. In the example quoted neither the carbon dioxide nor the chlorides showed as much departure from the normal as the average case of pyloric stenosis, and yet tetany in a fairly severe form occurred regularly. We have on only one occasion observed signs of tetany in congenital pyloric stenosis (laryngismus and a positive facial phenomenon).

Treatment for the fully developed case of gastric tetany is not wholly satisfactory. Relief of the causal pyloric obstruction when present is obviously indicated. In cases where the gastric dilatation and attendant vomiting cannot be dealt with surgically, tetany may be prevented, or, if present, relieved, by acid therapy, and in many instances even the liberal use of sodium chloride as normal saline may ward off attacks.

Hyperpnoeic Tetany.—This form of tetany can be most readily demonstrated by voluntary deep breathing (over-ventilation), although numerous cases have been recorded in which the condition has appeared as a clinical entity, occurring in hysterical patients or as a sequela of encephalitis lethargica.

By a short period of voluntary deep breathing the
free carbon dioxide is "washed out," and the result is the rapid production of a gaseous alkalosis. The same phenomenon has been produced by hot baths, which cause over-ventilation that is to some extent involuntary. The total carbon dioxide content will be diminished in contrast to the high total carbon dioxide content of the non-gaseous alkalosis found in gastric tetany. This alkalosis brings out the signs of tetany in the same way as in the gastric type.

The blood calcium tends to be high, and the inorganic phosphorus slightly diminished. The attack can be prevented or made to disappear by the administration of carbon dioxide gas, which will raise the free carbon dioxide content of the blood, and hence cause a disappearance of the alkalosis.

It will be seen then that both gastric and hyperpnoeic tetany are associated with a condition of alkalosis brought about in each case by entirely different means. In the former it is a non-gaseous alkalosis, and in the latter a gaseous one. In both, the total calcium content of the serum tends to be higher than normal, but the increased alkalinity of the blood presumably brings about a reduction in the ionised fraction. It may be argued that this theory as yet lacks sufficient confirmation, but its proof is difficult of accomplishment because of the technical difficulties in measuring accurately the ionised calcium fraction.

Administration of Alkali.—In normal subjects the ingestion of even large doses of alkali is unaccompanied by any obvious change in acid-base equilibrium. In children in whom there is some impairment of renal function as in nephritis or pyuria (Case V), or where there has been a recent upset in acid-base balance, e.g. acidosis in gastro-enteritis, the giving of sodium
bicarbonate may result in the development of a non-gaseous alkalosis, which is occasionally accom­panied by manifestations of tetany.

Case V.—E. McG., female, aged six months; admitted with pyuria and was given sodium bicarbonate fifteen grains four­hourly. After forty-eight hours on this treatment, convul­sions occurred. The blood chemistry at this time showed:

- Total carbon dioxide of blood .. 108.8 volumes per cent.
- Serum calcium .. .. .. 5.1 mgm. per cent.
- Non-protein nitrogen .. .. .. 50.0 mgm. per cent.

The sodium bicarbonate was discontinued and calcium chloride commenced. No more convulsions occurred.

TREATMENT OF TETANY

It is in connection with the treatment of tetany that an appreciation of the acid-base balance dis­turbances becomes of the utmost importance, and at the present time much confusion exists regarding the modus operandi of the acid treatment of tetany with such salts as calcium chloride.

Any form of tetany can be made to disappear by the production of an acidosis, no matter how this is brought about. One is familiar, for instance, with an attack of gastro-enteritis in a rachitic infant bringing about the disappearance of the signs of tetany, either active or latent, only to have these return later with the disappearance of the acidosis, which was induced by the gastro-enteritis (Cases VI and VII).

Case VI.—M. C., aged thirteen months; rachitic infant.

2.10.23.—Admitted with gastro-enteritis. Facial pheno­menon + + + : laryngismus + .

3.10.23.—Has been on water for past twelve hours. All signs of tetany gone.

- Total carbon dioxide of blood .. 34.5 volumes per cent.
- Serum calcium .. .. .. 3.8 mgm. per cent.
- Serum phosphorus .. .. .. 7.7 mgm. per cent.
5.10.28.—Since last note has had sodium bicarbonate, thirty grains four-hourly. Facial phenomenon +.

- Total carbon dioxide of blood .. 47·7 volumes per cent.
- Serum calcium .. .. .. 4·1 mgm. per cent.
- Serum phosphorus .. .. .. 5·1 mgm. per cent.

8.10.28.—The alkali treatment was continued. Facial phenomenon +++; laryngismus ++; Trousseau’s sign + +. 

- Total carbon dioxide of blood .. 68·1 volumes per cent.
- Serum calcium .. .. .. 3·0 mgm. per cent.
- Serum phosphorus .. .. .. 5·4 mgm. per cent.

Case VII.—R. C., aged twenty-two months; markedly rachitic infant.

14.12.23.—Admitted with tetany; facial phenomenon +++; laryngismus +.

15.12.23.—Developed an acidosis overnight, cause unknown. All signs of tetany gone.

- Carbon dioxide content of blood 38·1 volumes per cent.
- Serum calcium .. .. .. 9·5 mgm. per cent.
- Serum phosphorus .. .. .. 8·8 mgm. per cent.

18.12.23.—Since previous note has been on sodium bicarbonate, thirty grains four-hourly. Acidosis gone. Facial phenomenon +++; laryngismus +.

- Carbon dioxide content of blood 54·5 volumes per cent.
- Serum calcium .. .. .. 7·7 mgm. per cent.
- Serum phosphorus .. .. .. 3·2 mgm. per cent.

One would also in this connection recall Binger’s observation that although he was able to reduce the blood calcium with the acid phosphate salt, tetany did not develop. It also offers a satisfactory explanation of the absence of tetany in the majority of cases of chronic interstitial nephritis, showing uræmic signs with a low blood calcium. The theory of the acid treatment of tetany, then, is based on the hypothesis that the ionised calcium is increased in amount by the production of acidosis.

**Method of Production of the Acidosis.**—By giving an inorganic acid or certain salts of inorganic acids in proper amounts, one can so lower the bicarbonate content of the blood that there will be induced a mild
TETANY

non-gaseous acidosis presenting no clinical signs, but readily appreciated biochemically by the fall in the total carbon dioxide content of the blood to the region of 35 to 40 volumes per cent. The immediate effect of a fall of this extent in the carbon dioxide is to cause a rise in the total calcium content of the blood and also to render more of it ionised. With this rise in calcium the signs of tetany will disappear in a few hours, except perhaps the Chvostek's sign (facial phenomenon) which may persist for twenty-four or forty-eight hours.

Many acids or "acid-producing" salts have been used by various workers. Hydrochloric acid is the most commonly used acid, and is very efficient so far as adults are concerned. Its value in infants, however, is limited because of the tendency to vomiting which it produces. Ammonium chloride, ammonium phosphate, and calcium chloride are examples of the "acid-producing" salts. Ammonium chloride presumably is absorbed from the bowel unchanged, the ammonia radicle is converted into urea by the liver, and the chlorine left as hydrochloric acid to exert its acid effect. Ammonium phosphate acts similarly, but calcium chloride exerts its effect somewhat differently. Only a minimal amount of the calcium is absorbed as it is mainly excreted in the stool in combination with fatty acids as soaps; the chlorine radicle is absorbed without the calcium, and so exerts its acid effect.

The most satisfactory of these "acid-producing" substances is, to our mind, calcium chloride, since the ammonium salts throw an unnecessary and avoidable strain on the liver. In many ways it is unfortunate that the calcium salt is the most satisfactory since it tends to concentrate one's attention on the calcium fraction, and many believe that such a salt as the
lactate will be equally efficient. This, however, is not the case. Calcium lactate cannot be considered a satisfactory form of treatment for active tetany, since it has no acid-producing properties, the lactic acid being completely oxidised in the tissues.

**Treatment of Infantile Tetany.**—The acidosis produced by the giving of such "acid-producing" salts...
lasts only as long as the salts are being given. One can with calcium chloride bring about in a few hours a disappearance of all the dangerous manifestations of tetany, but in those infants in whom the tetany is associated with rickets the treatment must go further. The fundamental condition which predisposes to the tetany must also be dealt with. The retention of calcium in these infants is often greatly diminished, but can be increased three- or fourfold in a few days by giving an ample supply of vitamin D (cod liver oil or one of the proprietary preparations) (Figure XX). Once this has been accomplished it is safe to omit the calcium chloride, and rely on the increased retention to supply the necessary calcium. It should be mentioned here that by acid therapy the blood calcium is raised at the expense of the calcium in the bones and tissues, and hence it should be looked upon as an emergency measure.

In practice, a method of carrying out the above treatment which we have frequently used successfully is as follows:

(1) Calcium chloride, thirty grains four-hourly for three days only.

(2) Cod liver oil, a teaspoonful thrice daily.

The calcium chloride is discontinued after three days, but the cod liver oil is continued for a month at least, to ensure a satisfactory retention of calcium. Cod liver oil may, of course, be replaced by any other active preparation containing vitamin D. The following case is illustrative:

Case VIII.—Aged fifteen months.
14.10.25.—Admitted with convulsions. Facial phenomenon negative. No laryngismus. Trousseau's sign negative. Serum calcium 6.5 mgm. per cent. Given calcium chloride, thirty grains four-hourly and cod liver oil, a teaspoonful thrice daily.
17.10.25.—No convulsions since last note. Calcium chloride discontinued. Continued with cod liver oil.
18.10.25.—No convulsions; facial phenomenon +; no laryngismus or Trousseau’s sign.
28.10.25.—Still on cod liver oil. Very well. Facial phenomenon negative.

If the condition be only latent tetany manifested by a positive facial phenomenon or Trousseau’s sign, cod liver oil alone is probably sufficient, although it has occasionally been recorded that such a course has appeared to aggravate the tetany for a short period at the commencement of the treatment.

(We are indebted to Dr. Leonard Findlay for permission to publish Cases VI, VII and VIII.)
CHAPTER XV

PYLORIC STENOSIS

There is a tendency for attention to be focused on the mechanical factors in pyloric stenosis, the importance of which one cannot gainsay. There are, however, certain metabolic disturbances which also require consideration as they are of definite significance in diagnosis and treatment. In congenital pyloric stenosis and, indeed, in any obstruction of the upper part of the small intestine there is always present a well-marked non-gaseous alkalosis. The problem from the biochemical standpoint centres round chlorine, which plays an important part in all disturbances of acid-base equilibrium.

Biochemical investigations in obstruction of the pylorus have proved of the utmost importance in throwing light on the behaviour of the various elements of the blood in all disturbances of acid-base equilibrium. The earliest appreciation of these changes came from experimental work. In 1918, McCann showed that the carbon dioxide combining power of the blood plasma was greatly increased after the pylorus was ligated. Two years later, McCallum and his co-workers demonstrated the same phenomenon, and associated the rise in carbon dioxide with a fall in the chlorine content of the blood. The explanation they offered was that the chlorine deficiency is primary and due to a loss of chloride by vomiting of gastric juice; this, they
suggested, leads to a deficiency in the blood and tissue fluids of an acid radicle (chlorine) which necessitates the retention of another acid radicle (carbon dioxide) as a compensatory measure. Since then, numerous workers have obtained similar findings in duodenal and pyloric obstructions in man.

In general, it may be said that the blood chemistry in pyloric stenosis resembles the picture described in experimentally produced high intestinal obstruction (Figure XXI). We might say here that we believe the
condition of alkalosis to be present to some degree in practically every case. Table XVIII shows the usual findings in pyloric stenosis.

<table>
<thead>
<tr>
<th>TABLE XVIII</th>
</tr>
</thead>
</table>

**Respiration** .. .. .. Depressed.

**Blood**—
- Carbon dioxide content .. Increased.
- Chlorine content .. Reduced.
- Non-protein nitrogen content Increased.
- Fixed base .. .. .. Normal or slightly reduced.

**Urine**—
- Chlorine content .. .. Very much reduced.

**Metabolism**—
- Retention of chlorine administered parenterally (Table XXIII) .. .. .. Greatly increased.

According to Gamble, and most workers are in agreement with him, the primary disturbance in experimental high intestinal obstruction is the loss of chlorine in the vomitus. While we consider that the loss of gastric juice plays a part in the production of the symptoms and biochemical abnormalities in pyloric stenosis of infancy, we feel that to this alone cannot be attributed all the phenomena. This is not merely a question of academic interest since it has an important bearing on therapy. Before, however, dis-
cussing the pathogenesis of the disturbance in acid-base equilibrium we shall consider the various clinical and biochemical findings.

** CLINICAL MANIFESTATIONS **

A most striking and probably the only important clinical manifestation of the presence of alkalosis in pyloric stenosis is depressed breathing. This is present in one form or another in practically every patient with pyloric stenosis of any duration. The depressed breathing is evidenced in one of three ways. First, there may be a shallow type of respiration, so shallow, indeed, that even with the bell of the stethoscope placed in front of the nose and mouth it is often extremely difficult to hear the breathing. Secondly, the rate may be diminished, frequently to eight or ten respirations per minute. Thirdly, there may be well-marked and often alarmingly long periods of apnoea followed by three or four shallow respirations producing the typical Biot type of breathing. Most frequently all three manifestations are present together. It is not uncommon, however, for the respiration to be almost normal in rate over a period of a minute but shallow in depth with apnoeic periods occasionally appearing at longer intervals. This respiratory depression we consider an important diagnostic sign (Case IX).

** Case IX. — J. L., male, aged eight weeks. Normal labour; apparently healthy infant. Breast-fed; throve well, no vomiting; nothing unusual noted about the motions. For the past few weeks mother thought the infant was unduly quiet, "as if he were doped." She brought him to hospital because of this.**

On admission he was seen by Dr. Findlay, who observed that the respiratory rate was very depressed (twelve per minute), and the breathing shallow with apnoeic periods. Despite the
absence of any history of vomiting he was led to suspect pyloric stenosis, and on examination, typical gastric peristalsis was evident and a pyloric tumour easily palpated. The head was small and the infant appeared mentally backward. The blood carbon dioxide was found to be 102·0 volumes per cent. The child was in hospital for four weeks, during which time the condition remained unchanged, and he vomited only once. Death occurred following a sudden bout of fever. Post-mortem examination revealed defective development of the cerebral hemispheres and the presence of a well-marked hypertrophy of the pylorus.

Accompanying the diminished pulmonary ventilation there is general lethargy, giving one the impression that the infant is under the influence of some hypnotic drug. The patients are therefore not cross infants. Having taken a feed and vomited, they will at once take a repeat feed, which is generally retained. It is
interesting to note that in adults with marked pyloric obstruction there are symptoms such as lassitude and mental changes which have been ascribed to the presence of an alkalosis. This is most frequently the case when the patient, who has a duodenal ulcer, is undergoing intensive alkali therapy.

This respiratory depression is closely related to the carbon dioxide content of the blood, as can be seen from Table XIX and Figure XXII.

**Table XIX**

**SHOWING CORRELATION BETWEEN CARBON DIOXIDE CONTENT OF BLOOD AND RESPIRATORY RATE IN PYLORIC STENOSIS.**

<table>
<thead>
<tr>
<th>Average respiratory rate (per minute).</th>
<th>8</th>
<th>13·8</th>
<th>18·1</th>
<th>23·4</th>
<th>27·8</th>
<th>38·9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average carbon-dioxide content of blood (vol. units per cent.).</td>
<td>138·8</td>
<td>108·6</td>
<td>99·0</td>
<td>99·0</td>
<td>87·7</td>
<td>65·2</td>
</tr>
</tbody>
</table>

This correlation between respiratory rate and carbon dioxide content of the blood is the more remarkable when one remembers that it is the total pulmonary ventilation rather than the rate of breathing which is significant in determining, or being determined by the level of carbon dioxide in the blood. Thus it can be taken as a general rule that, regardless of the depth, the slower the respiratory rate, the greater is the increase in blood carbon dioxide. It may here be noted that this relationship does not hold good in infants when the respiratory depression is due to a cause other than pyloric stenosis (Table XX). The carbon dioxide content of the blood of infants in such
conditions as meningitis and congenital malformation of the heart is usually quite normal, although the respiratory rate may be as low as four per minute. One important point in the clinical differentiation of these two types of slow breathing is the presence or absence of cyanosis, cyanosis being a marked feature in the non-pyloric cases and invariably absent in pyloric stenosis.

**Table XX**

**Total Carbon Dioxide Content of Blood in Non-obstructive Cases with Reduced Respiratory Rate.**

<table>
<thead>
<tr>
<th></th>
<th>W.D. Congenital Heart Disease</th>
<th>J.L. Encephalitis</th>
<th>M.N. Cerebral Hemorrhage</th>
<th>R.M. Prematurity</th>
<th>J.G. Meningitis</th>
<th>M.C. Pyuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (per minute)</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>*10</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Carbon dioxide content of blood (vol. per cent.)</td>
<td>52.7</td>
<td>62.7</td>
<td>57.5</td>
<td>55.0</td>
<td>57.1</td>
<td>55.4</td>
</tr>
</tbody>
</table>

**BIOCHEMICAL FINDINGS**

The three outstanding changes observed in the blood are: (1) rise in the carbon dioxide content, (2) fall in the chlorine content, and (3) rather less frequently, a rise in the non-protein nitrogen value (Table XXI). The fixed base is usually within normal limits, but is occasionally reduced owing to loss of base in the vomitus.

The urine contains practically no chloride, the silver nitrate test yielding at most a very faint haze. The urinary reaction is in most cases alkaline, but an acid reaction is by no means uncommon.
Rise in the Carbon Dioxide Content of the Blood.—It will be remembered that this finding by itself signifies either non-gaseous alkalosis or gaseous acidosis. The carbon dioxide dissociation curve, as might be expected, is hypercapnic (page 32), showing a shift to the left, i.e. the capacity to hold carbon dioxide is increased, a finding characteristic of either of the above two conditions. Values for the actual pH of the blood have been obtained in a few instances, and invariably when there is any change, it is towards the alkaline side. This is in accord with what has been found in adult patients with high intestinal obstruction.

In contrast with the above the pH value of the blood in a patient suffering from encephalitis is of interest. Here, although the respiratory rate was only eight per minute, the pH was 7.25 (carbon dioxide, 67.0 volumes per cent.), indicating a gaseous acidosis which is caused by diminished respiratory activity. The pH values in pyloric stenosis and high intestinal obstruction make it clear that the disturbance of the acid-base balance is towards the alkaline side, and the
change in the respiratory volume is attributable, and therefore secondary, to alkalosis.

**Relationship of Carbon Dioxide to Vomiting.**—There is a general conception that the carbon dioxide content of the blood rises because of the loss of chlorine in the vomitus. The results of Gamble and others certainly afford strong evidence that such a theory is essentially correct for experimental obstruction in animals. Gamble showed that in rabbits, although vomiting did not take place, chlorine-containing fluid was secreted into the stomach and virtually lost as far as the circulating fluids were concerned. In congenital pyloric stenosis, however, there is not a close relationship between increase of carbon dioxide and severity of vomiting. We have encountered patients presenting a typical picture of alkalosis with raised blood carbon dioxide and depressed breathing either during a period in which no vomiting occurred or, as in Case IX, where there was a complete absence of vomiting.

Further evidence against the view that vomiting is the cause of the alkalosis is the finding that severe vomiting in such conditions as meningitis does not cause a rise in blood carbon dioxide at all commensurate with that found in pyloric stenosis. It may be, of course, that the composition of the vomitus is the deciding factor. Never, however, have we been able to demonstrate the presence of free hydrochloric acid in the vomitus of infants with pyloric stenosis. Furthermore, in the chemical examination of the vomitus nothing has been found to explain the invariable presence of alkalosis in pyloric stenosis and its absence in most other conditions accompanied by severe vomiting. The records of individual patients
show that the total carbon dioxide content is not closely associated with the severity of the vomiting. And finally, there does not seem to be any relationship between the level of the carbon dioxide and the length of time the vomiting has existed.

**FIGURE XXIII**

**SHOWING INCREASE IN WEIGHT AND FALL IN TOTAL CARBON DIOXIDE CONTENT OF BLOOD IN CASE OF INFANT, J. B., RECOVERING FROM PYLORIC STENOSIS.**

---

**Relationship of Blood Carbon Dioxide to General Nutrition.**—In the individual patient there is an undoubted association between the fall of the carbon dioxide content to normal and the increase in the weight of the infant. This is illustrated in Figure XXIII. An isolated observation on the carbon dioxide content of the blood, however, is of no value in
prognosis. Thus a high carbon dioxide content is not necessarily of graver significance than one moderately increased, although a further rise in the carbon dioxide during the course of illness does indicate an aggravation of the metabolic disturbance. A high carbon dioxide content, as indicating depressed action of the respiratory system, would favour the use of a local as against a general anaesthetic for surgical treatment. For practical purposes great depression of the pulmonary ventilation is a valuable indication of the degree of the metabolic disturbance.

The fall in carbon dioxide and the improvement in general nutrition are concomitant events; the latter cannot be said to be caused by the former. In some instances the high carbon dioxide content was reduced by various measures without a resultant improvement in the general condition. In one instance blood transfusion caused an immediate reduction of the carbon dioxide from 98 volumes per cent. to 70.2 volumes per cent.: four days later, however, the value had returned to 97.8 volumes per cent. Similarly, we have noticed that the administration of calcium chloride causes a diminution of carbon dioxide without accelerating the recovery process. We stress this because there is a tendency by some to consider that in all forms of acid-base disturbance a return of the carbon dioxide content of the blood to a normal value is the final proof of successful treatment. The important factor is the underlying metabolic disturbance. It is comparatively easy to raise or lower the carbon dioxide content by free administration of alkali or acid as circumstances indicate, but this is of little value unless the underlying metabolic upset is also favourably affected.
ACIDOSIS AND ALKALOSIS

CHLORINE METABOLISM

The four significant findings in this connection are: (1) reduction in blood chlorine, (2) absence of urinary chlorine, (3) excessive retention of chloride administered parenterally, and (4) depletion of tissue chlorine. In general, it may be said that the degree to which these abnormalities are present is roughly related to the severity of the vomiting. Certain important exceptions have, however, been met with in congenital pyloric stenosis, so that one cannot accept the loss of chlorine by vomiting as the sole cause of the abnormalities of chlorine metabolism.

Blood Chlorine.—The fall in the blood chlorine is generally proportional to the rise in the carbon dioxide content and the degree of alkalosis. Nevertheless, examples have been encountered in which the symptoms of alkalosis were present in spite of a comparatively normal value for blood chlorine (Table XXII).

### Table XXII

**SHOWING THE RELATIONSHIP OF THE BLOOD CHLORINE AND CARBON DIOXIDE IN CERTAIN CASES OF PYLORIC STENOSIS.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Chlorine Content of Blood (mgm. per cent.)</th>
<th>Carbon Dioxide Content of Blood (volumes per cent.)</th>
<th>Rate of Breathing</th>
<th>Vomiting</th>
<th>Urinary Chlorine</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.C.</td>
<td>260</td>
<td>100.8</td>
<td>20 (apnoea +)</td>
<td>Very frequent.</td>
<td>Nil.</td>
</tr>
<tr>
<td>J.J.</td>
<td>260</td>
<td>98.8</td>
<td>24</td>
<td>Occasional.</td>
<td>Haze.</td>
</tr>
<tr>
<td>J.B.</td>
<td>320¹</td>
<td>—</td>
<td>25</td>
<td>Frequent.</td>
<td>Present.</td>
</tr>
<tr>
<td>B.S.</td>
<td>320¹</td>
<td>107.0</td>
<td>21</td>
<td>Nil.</td>
<td>Nil.</td>
</tr>
<tr>
<td>R.S.</td>
<td>320¹</td>
<td>102.4</td>
<td>20</td>
<td>Very occasional.</td>
<td>Nil.</td>
</tr>
</tbody>
</table>

¹ Following intravenous administration of sodium chloride.
PYLORIC STENOSIS

We have also observed that the rise in the blood chlorine following intravenous administration of sodium chloride is not necessarily accompanied by a commensurate fall of carbon dioxide (R. S., Table XXII).

**Urinary Chlorine.**—It has already been remarked that in pyloric stenosis chlorine is present in the urine only in very minute amounts. This has been attributed to the impoverishment of the blood chlorine. In several instances, however, there has been a complete lack of urinary chlorine, although the value for blood chlorine was within normal limits (Table XXII). After operation urinary chlorine does not begin to increase for at least four or five days.

The absence of urinary chloride is of some diagnostic value, especially if this finding is obtained on several occasions. Certainly, when no chlorine is found in the urine of a young infant with expulsive vomiting, the

### Table XXIII

**SHOWING THE PERCENTAGE RETENTION OF PARENTERALLY ADMINISTERED CHLORINE IN INFANTS WITH PYLORIC STENOSIS DURING PERIODS OF MILD VOMITING OR ABSENCE OF VOMITING.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
<th>Amount of NaCl Injected gm.</th>
<th>Volume of Urine c.c</th>
<th>NaCl Excreted.</th>
<th>Percentage Retention Chlorine</th>
<th>Frequency of Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Per cent.</td>
<td>Total.</td>
</tr>
<tr>
<td>J.D.</td>
<td>24. 5.29</td>
<td>—</td>
<td>220</td>
<td>0.059</td>
<td>0.130</td>
<td>95.4</td>
</tr>
<tr>
<td></td>
<td>25. 5.29</td>
<td>1.08</td>
<td>170</td>
<td>0.105</td>
<td>0.179</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td>3. 6.29</td>
<td>0.99</td>
<td>800</td>
<td>0.012</td>
<td>0.099</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>4. 6.29</td>
<td>0.99</td>
<td>586</td>
<td>0.023</td>
<td>0.123</td>
<td>97.3</td>
</tr>
<tr>
<td>J.R.</td>
<td>27. 4.29</td>
<td>—</td>
<td>265</td>
<td>0.048</td>
<td>0.128</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>28. 4.29</td>
<td>0.54</td>
<td>336</td>
<td>0.070</td>
<td>0.232</td>
<td>80.7</td>
</tr>
<tr>
<td>C.C.</td>
<td>17. 3.29</td>
<td>—</td>
<td>232</td>
<td>0.0</td>
<td>0.0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>18. 3.29</td>
<td>0.99</td>
<td>350</td>
<td>0.047</td>
<td>0.164</td>
<td>85.4</td>
</tr>
<tr>
<td>R.M.</td>
<td>10.10.29</td>
<td>—</td>
<td>67</td>
<td>0.000</td>
<td>0.004</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>11.10.29</td>
<td>0.90</td>
<td>129</td>
<td>0.059</td>
<td>0.076</td>
<td>92.0</td>
</tr>
</tbody>
</table>
diagnosis of pyloric stenosis is the most probable one. And when, added to this, there is depressed respiration, the diagnosis becomes practically certain even when gastric peristalsis and a palpable pyloric tumour are not detected. Conversely, the presence of abundant urinary chlorine is definite evidence that the condition causing the vomiting is not pyloric stenosis.

**Retention of Chlorine after Parenteral Administration.**—If saline is administered intravenously to an infant with pyloric stenosis, over 80 per cent. of the amount

<table>
<thead>
<tr>
<th>Name</th>
<th>Diagnosis</th>
<th>Amount of NaCl Injected gm.</th>
<th>Volume of Urine c.c.</th>
<th>NaCl Excreted</th>
<th>Percentage Retention of Chlorine</th>
<th>Frequency of Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.B.</td>
<td>Inanition.</td>
<td>0.06</td>
<td>205</td>
<td>0.585</td>
<td>0.522</td>
<td>11.8 Frequent.</td>
</tr>
<tr>
<td>B.W.</td>
<td>Meningitis.</td>
<td>0.72</td>
<td>450</td>
<td>0.303</td>
<td>1.20</td>
<td>7.0 Frequent.</td>
</tr>
</tbody>
</table>

TABLE XXIV

**SHOWING THE PERCENTAGE RETENTION OF PARENTERALLY ADMINISTERED CHLORINE IN INFANTS WITH VOMITING NOT DUE TO PYLORIC STENOSIS.**

injected is retained, whereas in the normal infant, at most 50 per cent., and usually very much less, is retained (Tables XXIII and XXIV). This excess retention of chlorine may occur even when there has been no vomiting for several days, and the blood has its full complement of chlorine. Furthermore, with repeated administration of saline, this excessive retention continues and well-marked oedema may ensue.

**Depletion of Tissue Chlorine.**—A great part of the excessive retention of parenterally administered
PYLORIC STENOSIS

chlorine serves to make good the tissue depletion. The figures in Table XXV show that the tissues in the infant with pyloric stenosis contain about half the amount of chlorine normally found. But it is also clear from this table that in the cases to whom saline had been given intravenously or intraperitoneally, high values for tissue chlorine were obtained, exceeding

Table XXV

SHOWING THE CHLORINE CONTENT OF THE VARIOUS TISSUES OF THE INFANT EXPRESSED IN MILLIMOLS PER KILO FRESH TISSUE.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cases without Pyloric Stenosis (six)</th>
<th>Cases of Pyloric Stenosis to whom no Saline had been given (four)</th>
<th>Cases of Pyloric Stenosis to whom Saline had been given (four)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>54;5</td>
<td>38;2</td>
<td>43;2</td>
</tr>
<tr>
<td>Liver</td>
<td>45;0</td>
<td>25;0</td>
<td>36;5</td>
</tr>
<tr>
<td>Lung.</td>
<td>62;5</td>
<td>47;5</td>
<td>52;4</td>
</tr>
<tr>
<td>Heart.</td>
<td>41;0</td>
<td>32;7</td>
<td>37;7</td>
</tr>
<tr>
<td>Kidney</td>
<td>44;8</td>
<td>39;8</td>
<td>42;1</td>
</tr>
<tr>
<td>Brain</td>
<td>58;5</td>
<td>35;9</td>
<td>48;0</td>
</tr>
<tr>
<td>Skin.</td>
<td>47;7</td>
<td>32;6</td>
<td>38;2</td>
</tr>
</tbody>
</table>

in many instances the average or even the maximum obtained in infants without pyloric stenosis. Thus, the administration of saline is capable of raising the diminished tissue chlorine content to normal or even super-normal values. And the interesting point may be again mentioned that in the cases in which this has taken place, even to the production of oedema, the urine very often contains only a small amount of chlorine, and the carbon dioxide content of the blood does not fall.
RISE IN THE NON-PROTEIN NITROGEN CONTENT OF THE BLOOD

This is a common but not an invariable finding. It has led to the suggestion that renal function is impaired. On several occasions, however, the urea output has been estimated, and a normal percentage and total output have been found. Another theory put forward is that the retention of non-protein nitrogen is an attempt on the part of the organism to maintain the normal osmolar concentration. The chlorine and fixed base of the blood are very often both reduced, so that even if the loss of chlorine is made good by retention of carbon dioxide there is still a deficiency in osmolar concentration (acid + base + non-electrolytes such as urea and glucose). According to Hartmann and Smyth, the rise in non-protein nitrogen is one of the methods whereby this concentration is maintained at a normal level. The evidence so far obtained is not conclusive. There is, however, a third view, which we feel is worthy of consideration. Since the withdrawal of chloride from a diet causes an increased catabolism of nitrogenous substances, it may be that the disturbance of chlorine metabolism present in pyloric stenosis leads to a breakdown of tissue substance with consequent accumulation of nitrogenous products in the blood.

THEORIES AS TO THE PATHOGENESIS OF THE ALKALOSIS

The most popular theory is that elaborated by Gamble and his co-workers, namely, that the loss of chlorine by the vomitus is the primary factor, leading to a depletion of tissue and blood chlorine and a
consequent compensatory retention of carbon dioxide. Although fixed base and water are also lost in the vomitus, in view of the smaller store of chlorine than fixed base in the body, the amount of this element lost is relatively greater and therefore of more importance. We feel that this theory, although quite satisfactory for experimental ligature of the pylorus, does not explain all the phenomena of congenital pyloric stenosis of infants. Chief amongst our objections is the fact that alkalotic symptoms can occur even in the complete absence of vomiting and, also, that by supplying chlorine, the condition is not corrected.

Haden and Orr first suggested that the chlorine was fixed in the tissues by some toxin, and Drake and Tisdall have shown that injection of histamine, a substance elaborated in the gut, leads to a low blood chlorine not attributable to vomiting. It is feasible, therefore, that the primary cause of congenital pyloric stenosis is a disorder of the metabolic processes taking place in the pylorus, associated with hypertrophy, and leading to the elaboration of some histamine-like substance which, on absorption, causes abnormal metabolism of chlorine.

**THERAPEUTIC INDICATIONS**

From the practical point of view it would seem that there is definite indication for the administration of saline when there has been a considerable amount of vomiting. The continued giving of saline, however, is definitely contra-indicated owing to the risk of oedema. When an infant with pyloric stenosis is admitted to hospital in a state of very marked alkalosis with dehydration and lethargy, administration of saline is advisable, but it should be given with discrimination
and not pushed to the production of oedema. The operation risk may be very great, but whether operation is decided upon or not, restoration of the depleted chlorine reserves is of importance. This becomes all the more necessary when there is an excess of nitrogenous end-products in the blood, since, as has already been pointed out, a liberal supply of chlorine is necessary for normal nitrogen metabolism.

Another point in treatment is the avoidance of the use of alkali in gastric lavage or the employment of citrated milk in feeding, since it would appear rational to suppose that the additional alkali would aggravate the condition of alkalosis.

The question of operative or non-operative treatment is outwith the scope of the present discussion. We would, however, point out two considerations. Firstly, the recovery from alkalosis is always much more rapid when surgical measures are employed. The blood chemistry returns more quickly to normal after operation, although the urinary chlorine does not make its appearance for four or five days. Secondly, the choice of anaesthetic should depend upon the state of the acid-base equilibrium. If respiration is very depressed, a general anaesthetic should be avoided if possible.
CHAPTER XVI

THE RESPONSE OF SOME BLOOD CONSTITUENTS TO CHANGES IN ACID-BASE EQUILIBRIUM

It has already been pointed out that although the reaction of the blood ultimately depends on the relationship between free and combined carbon dioxide, this is but the final result of innumerable chemical changes. It is of advantage, therefore, to consider in a general way the behaviour of some of the more important constituents of the blood during disturbances of acid-base equilibrium.

WATER

Water is the most important single constituent of the living organism. Its regulation is "so to speak anxiously supervised by nature," and this is not surprising when one remembers that all chemical changes which are grouped under the term metabolism, refer to reactions in and between substances in solution. In the blood, lymph vessels and tissue spaces, the water exists "free" while within the cells the greater part is bound to colloids.

The daily requirement of water varies from 30 c.c. per kilo body weight in the adult to 150 c.c. in the infant. Of this the bulk comes from ingested water and only a fraction (about 5 c.c. per kilo) by oxidation of foodstuffs.
100 g. protein completely oxidised yield 41.8 gm. water
100 g. fat " " " 107.1 "
400 g. carbohydrate " " " 222.0 "
100 g. alcohol " " " 117.4 "

The excretion of water takes place mainly via the kidneys (60 per cent.). From 400 to 700 c.c. (average 22 per cent.) are lost through the sweat-glands, 260–360 c.c. (average 12 per cent.) through the lungs, and 100–200 c.c. (average 6 per cent.) in the faeces. The necessity for maintaining an adequate supply of water is made obvious from a consideration of this loss.

The following figures show the amounts required for the various digestive juices.

<table>
<thead>
<tr>
<th>Digestive juice</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>1000–1500 c.c.</td>
</tr>
<tr>
<td>Gastric juice</td>
<td>1000–2000 c.c.</td>
</tr>
<tr>
<td>Bile</td>
<td>600–900 c.c.</td>
</tr>
<tr>
<td>Pancreatic juice</td>
<td>600–800 c.c.</td>
</tr>
<tr>
<td>Intestinal juice</td>
<td>200 c.c.</td>
</tr>
</tbody>
</table>

The stability of the reaction of the blood is intimately associated with the regulation of water-balance. In health, a diet containing an excess of acid-producing substances leads to a lowered affinity of the tissues for water while an excess of base generally causes an increase in the volume of the tissues, although it may have the opposite effect. In pathological states, where complicating factors arise, the result may be confusing. The administration of hypertonic solutions, for example, is said not to produce diuresis if the carbon dioxide capacity of the blood is below 45 volumes per cent. When it is raised above this level the excretion of the stored water immediately takes place.

By the passage of water to and from the cells, the
RESPONSE OF SOME BLOOD CONSTITUENTS 171

osmotic pressure is regulated. It varies within narrow limits and quite a small departure from normal is sufficient to produce profound disturbances of cellular activity. The osmotic pressure is dependent upon the nature and concentration of dissolved substances, and any alteration is rectified by a movement of water or other substances to or from the blood.

A consideration of these facts shows the importance of making good the depleted supply of water so frequently met with in disturbances of acid-base equilibrium.

**CHLORINE**

Chlorine constitutes about two-thirds of the acid radicles of the plasma, and is an important constituent both of the tissue fluids and of the gastric juice. In the normal individual its secretion as free acid by the stomach produces a slight temporary alkalosis which is compensated for by an increased excretion of alkali in the urine (alkaline tide). Owing to its importance in the maintenance of the osmotic pressure of the tissue-fluids, chlorine is closely associated with the degree of tissue hydration. In general, it may be said that water cannot be stored in the body without its quota of chlorine. If for some reason excess chlorine is stored in the tissues, water is also retained and oedema results. Conversely, whenever there is depletion of chlorine, as after excessive sweating, ingestion of large amounts of water may lead to temporary retention of water in the tissues unaccompanied by the necessary chlorine. This may be manifested clinically by severe muscular cramps (Stoker’s Cramp).

As a general but by no means universal rule,
chlorine compensates for changes in the carbon dioxide content of the blood and *vice versa*. The fixed base content of the body fluids seldom alters to an appreciable extent and when carbon dioxide diminishes, the chlorine, other things being equal, rises to take its place. In pyloric stenosis, in which the chlorine of the blood and tissues is greatly diminished, we have one notable exception to this reciprocal change. By supplying chlorine in these cases to bring this acid radicle up to its normal level, the carbon dioxide is often not diminished in proportion. There is here another factor which, as yet, has not been discovered and further investigation is required. Nevertheless, generally speaking, this reciprocity of chlorine and carbon dioxide is one of the most important methods whereby both the ionic concentration and osmotic pressure of the blood and tissue-fluids are maintained at their normal levels. If, however, there is a very marked increase of other acid radicles, for example, keto-acids in diabetic coma, the chlorine may diminish together with the carbon dioxide. According to some workers, the chlorine may by its reduction keep the osmotic pressure normal when there is an increase of such non-electrolytes as urea. It is in this way that they explain the fall of plasma chlorine in chronic interstitial nephritis.

The free movement of chlorine between plasma and corpuscles has already been mentioned as the Ham-burger phenomenon (Chapter V), and it is enough here to stress its importance as a means whereby the plasma can make full use of the important buffering system in the corpuscles.

There are some problems connected with chlorine metabolism which still await solution. One of these
is the regulation of chlorine excretion. The chief route is the urine and Ambard, by devising a formula linking up salt excretion and plasma chlorine concentration, has indicated that there exists a renal threshold for chlorine. In diabetes and the terminal phase of nephritis, however, chlorine excretion continues after the plasma chlorine has reached values below the threshold. In pyloric stenosis, on the other hand, it is possible to raise the plasma chlorine content above the threshold value though the amount of chlorine in the urine remains infinitesimal. In encephalitis lethargica associated with increased pulmonary ventilation, the plasma chlorine rises without excessive amounts of chlorine appearing in the urine. The reason for the disappearance of chlorine in the urine of patients with lobar pneumonia has not yet been made clear. It is suggested that it is stored in the pneumonic exudate, but this is probably not correct. It seems more than likely, therefore, that although chlorine may behave as a threshold substance in health, it does not behave thus in many diseases.

The changes in blood chlorine in the various conditions attended by disturbance in acid-base equilibrium have been detailed in the corresponding chapters. It will suffice here to give a summary.

(1) **Non-Gaseous Acidosis.**—There is a shift of chlorine from plasma to red blood cells. When there is excessive production or retention of other acid radicles the plasma chlorine is reduced. But if there is great loss of water and base, as in diarrhœa, the concentration of plasma chlorine is increased. As a rule, acidosis has a diuretic effect which may be very marked and with the loss of water and base there is a loss of chlorine. In recovery from dehydration the
chlorine must be replaced *pari passu* with water; otherwise, the normal water content is not restored, or, if restored without chlorine, disturbances in the tissues may develop.

(2) *Gaseous Acidosis.*—The plasma chlorine is low because of the large shift of chlorine to the corpuscles.

(3) *Non-Gaseous Alkalosis.*—The plasma chlorine is as a rule low and the urine is almost free of chlorine.

(4) *Gaseous Alkalosis.*—If this has continued for any length of time the plasma chlorine is increased to compensate for the deficiency in carbon dioxide. Occasionally this increase in chlorine is prevented by vomiting or by chlorine starvation, in which case the alkalosis becomes very marked, the ionic calcium is reduced in amount, and tetany ensues.

**PHOSPHORUS**

Phosphates are important buffers in the blood, and their most important stabilising effect on acid-base equilibrium is the saving of base effected by their excretion in the urine as the acid instead of the alkaline salt. The more acid the contents of the small intestine, the better is the absorption of phosphorus. As a general rule, acidosis of any type increases the absorption and urinary excretion of phosphorus, while alkalosis tends to have the opposite effect. If sufficiently prolonged and in the absence of impaired renal function, a non-gaseous acidosis causes a fall of the inorganic phosphorus of the serum, possibly because of its ready excretion; a gaseous alkalosis has the same effect. A non-gaseous alkalosis and a gaseous acidosis each tend to produce a rise in the inorganic phosphorus of the serum.
RESPONSE OF SOME BLOOD CONSTITUENTS

It is improbable that a retention of phosphorus in the blood is ever the cause of acidosis, although this has frequently been suggested in nephritis. In this disease the high inorganic phosphate of the blood is probably only evidence of the kidney's inability to excrete phosphorus.

PROTEIN

At the pH of the blood the plasma proteins act as weak acids and normally combine with rather more than 10 per cent. of the total base. As the pH falls, there is a diminution of the base-combining power of the protein.

In alkalosis there is a transference of water from cells to plasma, and this by dilution causes a reduction of plasma protein. Acidosis, on the other hand, by its dehydrating effect, leads to an increase in protein concentration. In certain conditions associated with inanition, when the dehydration is remedied, the concentration of protein may fall below normal owing to an absolute deficiency. The lack of protein causes a diminution in the water-holding capacity of the plasma so that water passes from the plasma to the tissues. This probably explains the tendency to oedema in patients with marked wasting who have recovered from acidotic conditions such as diabetes or gastro-enteritis; for in these patients water is retained with avidity, and the plasma proteins, which have been diminished in amount, are insufficient to hold the newly acquired water, which is transferred to the tissues thus producing oedema, the so-called "nutritional oedema."
The amount of total base present in the plasma is constant, and this constancy is one of the most important features of acid-base equilibrium. It seems to be a matter of the greatest importance to the organism that the amount should not vary outside comparatively narrow limits. Peters and Van Slyke point out that every fluid and tissue has its own optimum content of each base, and that the organism strives to maintain this at a constant level.

The chief bases of the blood are sodium, potassium, calcium, and magnesium. Other elements present, such as iron and copper, although of great importance in other respects, are present in such small amounts that they need not be considered in connection with acid-base equilibrium. The two chief basic constituents of the fluids and soft tissues are sodium and potassium. Of these sodium forms over 90 per cent. of the base in the extracellular fluids, whilst within the cells potassium is predominant. There is no shift of base from corpuscles to plasma or vice versa, as occurs with acid radicles.

Maintenance of Concentration of Fixed Base.—The fixed base plays a most important part in the maintenance of a constant osmotic pressure of the body fluids. Ordinarily, changes in base and water content run parallel. Retention of base leads to retention of water, while withdrawal of water leads to a loss of base. If the fluid withdrawn is extracellular in origin, the diminution of base affects sodium while loss of intracellular water entails a drain on potassium. The concentration of fixed base (amount of base per litre) and the relative amounts of individual bases do not
vary much even when there is great disturbance in the distribution of acid radicles. Occasionally, as in terminal nephritis and in gastro-enteritis, there is a diminution of total base, while increases have been reported in nephrosis. These variations from the normal rarely if ever exceed fifteen per cent., which is small compared with the variations of chlorine or carbon dioxide observed in certain pathological conditions.

The means whereby the total base concentration is maintained within relatively narrow limits may here be briefly summarised. (1) Regulation by the volume of urine. When large amounts of water are absorbed, the volume of the urine is increased and its solid content decreased; this prevents the plasma and tissue fluids from becoming diluted. On the other hand, when a neutral salt is given with the ingested water, increased amounts of acid and alkali are excreted with the excess water. (2) In alkalosis, carbon dioxide combines with the excess base to form bicarbonate. This is usually excreted even when other substances such as chlorine are completely retained. If, however, renal function is impaired, as in pyuria or nephritis, the excretion of bicarbonate may be interfered with. (3) In acidosis, the fixed base is spared by excretion of the excess of free acid (titratable acid), and the formation of ammonia by the kidney.

CALCIUM

The absorption of calcium is promoted by any condition producing a more acid reaction in the small intestine, the insoluble calcium phosphate, carbonate, and soaps being changed into soluble calcium salts.
Administration of alkali is stated to have the opposite effect, though we have never been able to demonstrate this. Calcium is said to be present in the serum in three forms: (1) bound to proteins (colloidal), (2) dialysable but not ionised, and (3) ionised. Of these, the ionised moiety is of the greatest importance in the regulation of nerve-excitability. Any shift of the pH of the blood to the acid side will increase the amount of ionised calcium, whereas an increased alkalinity will lead to a decrease. If, prior to the onset of acidosis, the total serum calcium is below normal, the development of acidosis will lead not only to an increase in the ionised moiety but also to a rise in the total calcium of the serum.

GLUCOSE

While glucose itself is a neutral substance and therefore cannot compensate for abnormalities in the acid-base equilibrium of the blood, it must not be forgotten that the variations in carbohydrate metabolism have indirectly an important influence on acid-base balance. Glucose, moreover, is probably of importance in the maintenance of a normal osmolar concentration.

Defective carbohydrate oxidation leads to increased protein metabolism with an increased production of acid and, at the same time, to incomplete oxidation of fat with the formation of the acid ketone bodies.

It is commonly believed that acidosis itself interferes with glucose metabolism, for it is well known that in ketosis there is a diminution in sugar tolerance. The blood-sugar curve, starting below normal, rises after the ingestion of glucose to an abnormally high level, and the rise is unduly prolonged (Figure XVII).
Gilchrist, at the Royal Hospital for Sick Children, Glasgow, has shown that it is not acidosis itself which causes this, for, if acidosis is produced by the administration of ammonium chloride, the blood-sugar curve does not depart from normal in the same way as it does in ketosis. It is either the ketosis itself or the deficiency in glucose so frequently associated with ketosis which is the cause of the disturbed carbohydrate metabolism.
APPENDICES

APPENDIX I

KETOCgenic - ANTIKETOCgenic VALUES OF FOODS

FOODSTUFFS may be divided into two groups: (1) ketogenic, those capable of producing ketone bodies on catabolism, and (2) antiketogenic, those which prevent the production of ketone bodies. Each gramme of carbohydrate yields one gramme of antiketogenic substance, while each gramme of fat yields nine-tenths of a gramme of ketogenic and one-tenth of a gramme of antiketogenic substance. Protein leads to the production of 0.58 grammes of antiketogenic and 0.46 of ketogenic substance. Therefore, the ketogenic substances produced by any diet may be calculated from the formula,

$$K = 0.9F + 0.46P$$

and the antiketogenic from the formula,

$$A_K = 1C + 0.58P + 0.1F.$$  

F, P, and C represent grammes of fat, protein, and carbohydrate respectively. The ketogenic-antiketogenic ratio is shown by the formula,

$$\frac{K}{A_K} = \frac{0.9F + 0.46P}{1C + 0.58P + 0.1F}.$$  

In actual practice the following formula is sufficiently accurate.

$$\frac{K}{A_K} = \frac{F + P/2}{C + P/2}.$$  

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When the ketogenic-antiketogenic ratio is above 1.5:1, ketosis is usually produced. For therapeutic purposes, 4:1 ratios are desirable, but in no case should the daily intake of carbohydrate be below 10 grammes.

Table XXVI in this Appendix shows the caloric and keto- and antiketogenic values for 100 grammes of various foodstuffs.

**ACID-BASE VALUES OF FOODS**

In practical therapeutics it is becoming increasingly important to regulate the potential acidity or alkalinity of the diet. Sherman and Gettler (*Journ. Biol. Chem.*, 1912, XI, 323) showed that on the inorganic constituents of the diet depended its acidity or alkalinity, and that the nature of these constituents determined the amounts of acid and ammonia excreted by the urine, if it is assumed that the organic acids of certain fruits are completely oxidised. Consequently, it is possible to determine the potential acidity or alkalinity of a diet if its contents of acid and alkaline radicles are known. We have shown in Table XXVI the amounts of acid and alkali in terms of normal solution contained in the various foodstuffs. The difference between the two gives the potential acidity or alkalinity.

**APPENDIX II**

**PREPARATION OF SOLUTIONS**

**Normal Saline.**—Normal or physiological saline is prepared by dissolving 0.9 grammes of pure sodium chloride in each 100 c.c. of distilled water. Tablets containing the requisite amount may be obtained from
The ash constituents considered in this calculation were calcium, magnesium, sulphur, and phosphorus (divalent), and sodium, potassium, and chlorine (monovalent). The composition of the various foodstuffs was taken from Sherman's tables, *Chemistry of Food and Nutrition*, New York, 1928.
several of the drug houses. The solution is sterilised by boiling for from three to five minutes.

This solution may be given intravenously, intraperitoneally, or subcutaneously. Its use is indicated in all conditions of dehydration from whatever cause. In children the intraperitoneal route is in our opinion the most satisfactory, and in extreme cases the injection may be repeated once or twice in the twenty-four hours, or combined with intravenous administration.

**Hartmann's Solution.**—This solution has been recommended by Hartmann, as it not only supplies the water and chlorine but, in addition, bicarbonate, and an antiketogenic substance. It is prepared as follows:

Into a litre flask measure 60 c.c. lactic acid (C.P. 85 per cent.). Add a small amount of phenol red indicator (to show colour change), and neutralise with strong carbonate-free sodium hydroxide. Then add 10 grammes potassium chloride and 5 grammes of calcium chloride (CaCl$_2$·2H$_2$O). Make up to a litre with freshly distilled water. Boil for thirty minutes to hydrolyse the lactic acid: reneutralise with NaOH as often as the solution becomes acid. Bring back to original volume, filter, and measure into test tubes; sterilise under pressure in autoclave and seal the tubes.

Before using the solution, dilute twenty-five times (i.e. 10 c.c. to 250 c.c.) with freshly distilled sterile water.

This solution is used in the same manner as normal saline. The sodium lactate, as well as providing an antiketogenic substance (glucose) by synthesis, yields on oxidation, sodium bicarbonate.

**Glucose Solution.**—Glucose (dextrose) solutions may be either 5 per cent., which is isotonic, or stronger.
Ten per cent. solutions are recommended, because with this percentage proportionately greater amounts of glucose are retained in the body.

Ten grammes of pure glucose are dissolved in each 100 c.c. of freshly distilled water. It is best to use this solution within twenty-four hours of preparation. Sterilisation can be accomplished by boiling for from five to eight minutes.

The solution may be used either intravenously, intraperitoneally, or subcutaneously. It is preferable, however, to restrict its use to the intravenous route. The close proximity of the bowel with the risk of infection makes its use by the intraperitoneal route in any but exceptional circumstances undesirable. The danger of subcutaneous use is also one of infection.

It has the advantage over saline of providing in the glucose a food which is readily utilised.

**Glucose in Normal Saline (Dextro-saline).**—This is preferably used as a 10 per cent. solution, and is prepared by dissolving 10 grammes of glucose in 100 c.c. normal saline.

It is used in a similar way to the glucose solution, but with greater advantage because it supplies three substances of value to the acidotic and dehydrated subject, namely, water, sugar, and sodium chloride.

**Sodium Bicarbonate Solution.**—On heating, the bicarbonate of this solution becomes gradually converted into the irritating carbonate. It may, however, be satisfactorily prepared as follows. By means of a sterile spoon, pure sodium bicarbonate is added to boiled and cooled water in the proportion of one level teaspoonful of sodium bicarbonate to each 100 c.c. water. This makes, roughly, a 4 per cent. solution. It is only suitable for intravenous therapy, and its use
should be restricted to cases of extreme acidosis. On no account should it be mixed with glucose solution. For more accurate preparation, a 4 per cent. solution of sodium bicarbonate in water can be prepared and sterilised by boiling. The sodium carbonate can then be reconverted into bicarbonate by bubbling carbon dioxide through the solution when cool.

APPENDIX III

MOLAR AND NORMAL SOLUTIONS

A molar solution \( \frac{M}{1} \) of any substance contains in 1 litre the molecular weight of the substance expressed in grammes.

A millimol (mM) is one-thousandth of the molecular weight in grammes, which is the same as the molecular weight in milligrammes, and is contained in 1 c.c. of a molar solution.

Example.

\[ \text{NaCl} \frac{M}{1} \text{ solution contains } 58.5 \text{ gm. per litre.} \]

Therefore, 1 millimol = 58.5 mgm.

In the case of a gas, the molecular weight in grammes occupies 22.4 litres at 0° C. and 760 mm. Hg. (N.T.P.). Therefore, one millimol of any gas occupies \( \frac{22.4}{1000} \) litres, i.e. 22.4 c.c. at N.T.P.
Example.

60 vol. per cent. CO₂ = \( \frac{60}{22.4} \) mM per 100 c.c.

= 2.68 mM per 100 c.c.

= 26.8 mM per litre.

A normal solution \( \left( \frac{\text{N}}{1} \right) \) of any substance contains in 1 litre of solution the equivalent weight of the substance expressed in grammes. A decinormal solution \( \left( \frac{\text{N}}{10} \right) \) is one-tenth of the strength of a normal solution.

Example.

\[ \text{HCl} \quad \frac{\text{M}}{1} \text{ solution contains } 36.5 \text{ gm. in 1 litre.} \]

\[ \frac{\text{N}}{1} \text{ solution contains } 36.5 \text{ gm. in 1 litre.} \]

because the valency is 1.

\[ \text{H}_2\text{SO}_4 \quad \frac{\text{M}}{1} \text{ solution contains } 98 \text{ gm. in 1 litre.} \]

\[ \frac{\text{N}}{1} \text{ solution contains } 49 \text{ gm. in 1 litre.} \]

because the valency is 2.

A milli-equivalent (m-Eq) is one-thousandth of the equivalent weight in grammes, and is contained in 1 c.c. of an \( \frac{\text{N}}{1} \) solution, or 10 c.c. of an \( \frac{\text{N}}{10} \) solution.

Example.

\( \text{H}_2\text{SO}_4 \) has a molecular weight of 98 and a valency of 2.

The equivalent weight is 49.

1 milli-equivalent = 49 mgm.

A milli-equivalent of a monovalent substance is clearly the same as a millimol.
# Table XXVII

**Acid-base composition of plasma of venous blood.**

(Adapted from Harrison, *Chemical Methods in Clinical Medicine*, London, 1930.)

<table>
<thead>
<tr>
<th>Acid</th>
<th>Milli-Eq. per 100 c.c.</th>
<th>Milli-Eq. per litre or c.c. N/10 per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined carbonic acid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphoric acid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphuric acid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins and organic acids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total acid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Base.</th>
<th>mgm. per 100 c.c.</th>
<th>Milli-Eq. per 100 c.c.</th>
<th>Milli-Eq. per litre or c.c. N/10 per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium.</td>
<td>(1)</td>
<td>330</td>
<td>14·34</td>
</tr>
<tr>
<td>Potassium.</td>
<td>(1)</td>
<td>20</td>
<td>0·51</td>
</tr>
<tr>
<td>Calcium.</td>
<td>(2)</td>
<td>10</td>
<td>0·60</td>
</tr>
<tr>
<td>Magnesium.</td>
<td>(2)</td>
<td>5</td>
<td>0·25</td>
</tr>
<tr>
<td>Total Base.</td>
<td></td>
<td></td>
<td>16·60</td>
</tr>
</tbody>
</table>

(The figures in brackets indicate the valency of the various substances.)
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