ACIDOSIS

CLINICAL ASPECTS AND TREATMENT WITH ISOTONIC SODIUM BICARBONATE SOLUTION

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To my teacher D. D. Van Slyke
with sincerest gratitude
and admiration

Preface

»There is no reason why every patient should not reap the benefit of the simple methods which are now available for the analysis of blood.«

J. P. Peters and D. D. Van Slyke.

The object of the present book is to spread the knowledge of acidosis and of the treatment of this often dangerous complication with isotonic sodium bicarbonate solution, a therapy which the author had the pleasure of introducing into Denmark in 1934.

In spite of the fact that acidosis is a frequent and serious condition which annually, directly and indirectly, causes numerous deaths, the realisation of the significance of its treatment is not as yet very widespread. The reason why the treatment of acidosis has not become the common property of physicians in the same way as other rational therapies is to be found in several circumstances. The chief reason is no doubt that the clinical symptoms of acidosis, even in its fairly severe degrees, are frequently uncharacteristic, so that often the diagnosis can only be made with certainty by means of laboratory analyses. This renders it necessary to know exactly in what diseases and under what circumstances acidosis may be expected to be found, but here we meet with the difficulty that while several exhaustive theoretical expositions are available the clinical and therapeutic observations as a whole are not easily accessible in the literature. To this must further be added the fact that the form of exposition and the symbols used in the biochemical publications are usually so technical that the comprehension is rendered difficult or impossible to the reader who is not mathematically trained. As a last fact of importance I may finally mention that the clinical laboratory technique and the study of that branch of science is as yet rather undeveloped in this country.

The present book aims at giving a connected exposition for the use of hospital physicians and general practitioners of the clinical aspect and treatment of acidosis, based partly on the available literature, partly on the author's own observations. It is the author's conviction that a rational consistent adherence to the diagnosis and treatment of acidosis may contribute to save the lives of more than a hundred patients in Denmark annually.

Holstebro, Denmark, 1942. ESBEN KIRK.

Preface to the English Edition

After the appearance of the Danish edition of the present book the author has had the pleasure of seeing the treatment of acidosis with isotonic sodium bicarbonate solution widely adopted throughout the Scandinavian countries. The present English edition, the publication af which has been delayed by the war, contains a few new sections necessitated by the development during the last four years.

Holstebro, Denmark, 1946. ESBEN KIRK.

Brief Survey of the History of Acidosis and of its Treatment

The history of acidosis is a fascinating tale of the attainment of clarity in a important field, which constitutes a borderland between medical science and biochemistry. The subject seems especially to have attracted the prominent biochemists of the last generation (Henderson, Sørensen, Hasselbalch, Haldane, Van Slyke, Warburg), with the result that this section of biochemistry has been thoroughly developed theoretically.

The clinical investigation of acidosis dates considerably farther back than the theoretical and chemical study, viz. well over a hundred years, to O'Shaughnessy's researches during the cholera epidemic in London in 1831–32. In a short paper, »Experiments on the Blood in Cholera«, O'Shaughnessy[154] pointed out that on examining the blood of cholera patients he had found the salt and alkali content much reduced, and he added that he had found these salts again, and especially the sodium carbonate, in large quantities in the watery stools of the patients. O'Shaughnessy's findings soon gave rise to the treatment of cholera by intravenous injection of watery salt and soda solutions, a therapy which was first employed by a general practitioner at Leith, Dr. Latta. Latta's[112] reports in The Lancet express enthusiasm for the as a rule excellent results obtained by the new treatment, which was soon adopted in several quarters. With the termination of the epidemic the interest in intravenous treatment again waned, and the therapy seems almost to have been forgotten when the cholera again ravaged London in the fifties.[210]

It was actually Walter's[224] investigations (1877) on experimental acidosis that reawakened the interest in the problem of acidosis. Walter demonstrated the occurrence of a characteristic form of dyspnea following injection of dilute hydrochloric acid into rabbits, and pointed out the possibility

of calling even almost moribund animals to life again by the injection af sodium carbonate; this in connection with Kussmaul's[108] description in 1874 of a pronounced air-hunger in diabetic coma, »die grosse Athmung«, formed the background for Stadelmann's[202] demonstration of the fact that an acid poisoning occurs in diabetic coma (1883). For the treatment of fully developed diabetic coma Stadelmann suggested intravenous injection of a 2–3 p. c. solution of sodium carbonate and was thus the first to adopt the injection of unmixed alkaline solutions to combat acidosis. During the next 25 years the interest in alkaline treatment of this form of coma was lively. Even though it is approximately correct that, as pointed out by Hanssen[62] in 1910, the number of patients with fully developed diabetic coma whose lives had been saved by a bicarbonate therapy, could still at that period be written with one figure, these few cures of a form of coma previously regarded as hopeless, have been of signal importance for the understanding of the problem and the therapy of acidosis. At about the same time it was realised that in infantile diarrhea[33] and in uremic coma, too, serious acid poisoning was often present. Owing to the usually unfavourable prognosis for the chronic renal disease the renal form of acidosis never attracted the attention of physicians as much as the diabetic acidosis.

In the decade 1910–1920 the clinical investigation of acidosis attained a wider recognition. From this period date Sellards'[195, 198] brilliant results in his treatment of cholera on the Philippines by intravenous injection of bicarbonate solutions, and from the same time we have Marriott and Howland's[79, 80] significant publications on acidosis in infantile diarrhea. Sellards' treatment was later carried on by Rogers[177] in India, which resulted in a considerable reduction in the mortality from cholera. A very considerable advance followed the publication by Van Slyke and Cullen[219] in 1917 of a practical clinical method for the determination of carbon dioxide in the plasma. It is hardly too much to say that this method, which put the analysis into the hands of hospital physicians, has been of decisive importance for the more detailed clinical elaboration of the acidosis problem. There was still, in the years that followed, much uncertainty concerning the optimal concentration of the bicarbonate solutions employed. There seems to have been a marked tendency to use comparatively concentrated solutions as it was not yet understood that it

was necessary to treat at the same time the dehydration which was present. Even though the momentary effect of the treatment was often indubitable, the final results were in many cases less satisfactory.

In 1922 insulin treatment of diabetes was introduced by Banting and Best and medical science was enriched by one of the most important means of fighting acidosis. Even though it is hardly possible to overrate the value of insulin treatment, it should nevertheless be pointed out in this connection that the impressive efficiency of the insulin therapy has caused too great a loss of interest in the alkali treatment of diabetic coma. The striking clinical picture of that affection, and the usually excellent effect of insulin treatment, have impressed most students and physicians to such an extent that their attention has been diverted from other less conspicuous but frequent and often very grave conditions of acidosis. The period after 1922 has therefore in the main been marked by the insulin therapy in its various forms. In American pediatry, however, clinical investigations on the alkali treatment of infantile diarrhea have been carried on, though with varying intensity, and the treatment with sodium lactate introduced by Hartmann[70] in 1930 seems lately to have gained an increasing number of adherents. It is especially Van Slyke (1934)[216] who has emphasised the value of using an *isotonic* sodium bicarbonate solution, a therapy which has been adopted quite extensively by Cullen[32] in Cincinnati. As was pointed out in the preface, the parenteral alkali therapy in spite of its excellent effects is still as a whole very little known. In 1934 the author introduced the treatment with isotonic sodium bicarbonate solution into European clinical medicine.

I

Introduction

1. Definition of the Term Acidosis.

By the term acidosis is meant a condition in which the degree of acidity of the blood and the tissue fluids is increased. Acidosis never occurs as a separate disease but only as a complication. Its deleterious effects are due to the fact that the increase in the degree of acidity in the tissue fluids brings about changes in the function of the cells and eventually destruction of the same. These changes may be of so grave a nature that acidosis becomes the actual cause of death, probably owing to paralysis of the cells of the respiratory centre.

The term acidosis was first used by Naunyn (1906)[147] in a discussion of diabetic ketonemia. The concept has later quite correctly been extended to include other forms of the accumulation of acid in the body and such cases in which, owing to loss of alkali (e.g. in severe diarrhea and intestinal fistulas), an increase in the acidity of the blood occurs. It is of historical interest that it was the latter form of acidosis which first attracted the attention of clinicians and gave rise to the introduction of the intravenous alkali therapy (O'Shaughnessy and Latta 1831–32).

The determination of the degree of acidosis can be made by direct measurement of the degree of acidity of the plasma (the hydrogen ion concentration), a quantity which, at the suggestion of the Dane S. P. L. Sørensen, is usually expressed by the sign pH*). This measurement, with the simplified methods now available, can be made in any well equipped hospital laboratory.

An expression for the degree of acidosis still simpler than the pH of the plasma is, however, as pointed out by Van Slyke and Cullen[219] *in 1917, the total carbon dioxide content of the*

*) Normal value 7. 35—7. 51.

plasma, since this value will be reduced in all cases of acidosis which are of practical clinical importance).* The content of carbon dioxide in the plasma closely follows the variations in the total content in the organism of acid-binding factors and thus becomes a reliable measure for the degree of acidosis. For a staff not specially trained the analysis has fewer possibilities of error than the measurement of the pH and forms a more convenient foundation than the pH value for the calculation of the amount of alkali needed for the treatment of the acidosis. In the analysis for carbon dioxide which is made by shaking the sample with lactic acid in vacuum, besides the amount of carbon dioxide derived from bicarbonate, the so-called »bound« carbon dioxide, the determination will also include the amount of carbon dioxide physically dissolved in the plasma, the so-called »free« carbon dioxide. The amount of free carbon dioxide is, however, so small, c. 5 p. c. of the total amount of carbon dioxide, that in practice no great error is committed by regarding the whole as bicarbonate. *From the above statement it will appear that acidosis in a clinical sense may be defined as a condition in which the bicarbonate content of the plasma is reduced, and that the only laboratory analysis necessary for the determination of the presence and degree of the acidosis is the analysis of the bicarbonate of the plasma.* In our exposition the term »plasma bicarbonate« will be used to denote the total carbon dioxide content of the plasma, this term being preferable to the frequently employed but less accurate expression »alkali reserve«.

The determination of the total carbon dioxide content of the blood as an expression of its content of alkali was first employed by Walter[224] in 1877 in his famous work on experimental acid poisoning. Before the introduction by Van Slyke and Cullen of the determination of the plasma bicarbonate into the clinic in 1917, the determination of the carbon dioxide content in the exhaled air was a frequently

*) In lung diseases with difficult respiration and in other conditions with reduced pulmonary function (e. g. under premortal conditions) an accumulation of carbon dioxide in the blood, a carbonic acid acidosis, is sometimes seen, which is not accompanied by any reduction in the content of bicarbonate, but is frequently associated with a considerable increase of the hydrogen ion concentration, expressed by a reduction of the pH value. Conversely, in hyperventilation the removal of large amounts of carbon dioxide by the lungs may cause a reduction in the total carbon dioxide content of the plasma which is not indicative of an acid poisoning.

used method for the diagnosis of the presence and degree of acidosis. The determination is based on the fact that the carbon dioxide content of the exhaled air varies approximately as the bicarbonate content of the plasma. In the practical developments of Fridericia[50] and Marriott[128] the method was widely adopted and has been of great value in the early clinical elaboration of the acidosis problem. Since, however, the collection of the gas samples requires no little collaboration on the part of the patient, a collaboration which it is difficult to obtain from very exhausted patients, and since, further, the results give a much less accurate picture of the bicarbonate content of the plasma than the direct determination, the method has now in the main been abandoned. The historical significance of the analysis, is, however, incontestable.

The normal bicarbonate concentration in the plasma (and the serum) is 22–30 millimols or milliequivalents*) per litre. The bicarbonate content of total blood is lower than that of plasma, the bicarbonate concentration of the red blood cells being only six-tenths of that of the plasma. The term millimol has to a great extent superseded the earlier much employed expression of the bicarbonate content in volume per cent (vol %) of carbon dioxide. The use of the term millimol is, however, more convenient, for in investigations on the acid-base equilibrium it is an advantage to be able to express the acid and basic elements in the same and thus comparable values. A recalculation of millimol carbon dioxide per litre of plasma to vol % can, however, easily be made, since vol % carbon dioxide = millimol · 2.3.

Bicarbonate (carbonic acid) is a weak acid, the amount of which normally constitutes about $^1/_6$ of the acid constituents (total acid) of the plasma (see Fig. 1). *It possesses the conspicuous property that it can neutralise stronger acids, bicarbonate being thus split into carbon dioxide and water.* The neutralisation takes place almost instantly. The separated carbon dioxide is removed by the lungs while the invading acids replace the bicarbonate. The greater the amounts of invading acids are, the less will be the amount of bicarbonate remaining in the plasma (see Fig. 1, accumulation of acid).

*) One millimol is 1/1000 part of a gram molecule, i. e. the molecular weight expressed in mg. 1 millimol of carbon dioxide (CO_2) is thus 44 mg of carbon dioxide. By a milliequivalent is meant the millimol value divided by the valency. Carbonic acid being monovalent, 1 millimol of bicarbonate = 1 milliequivalent.

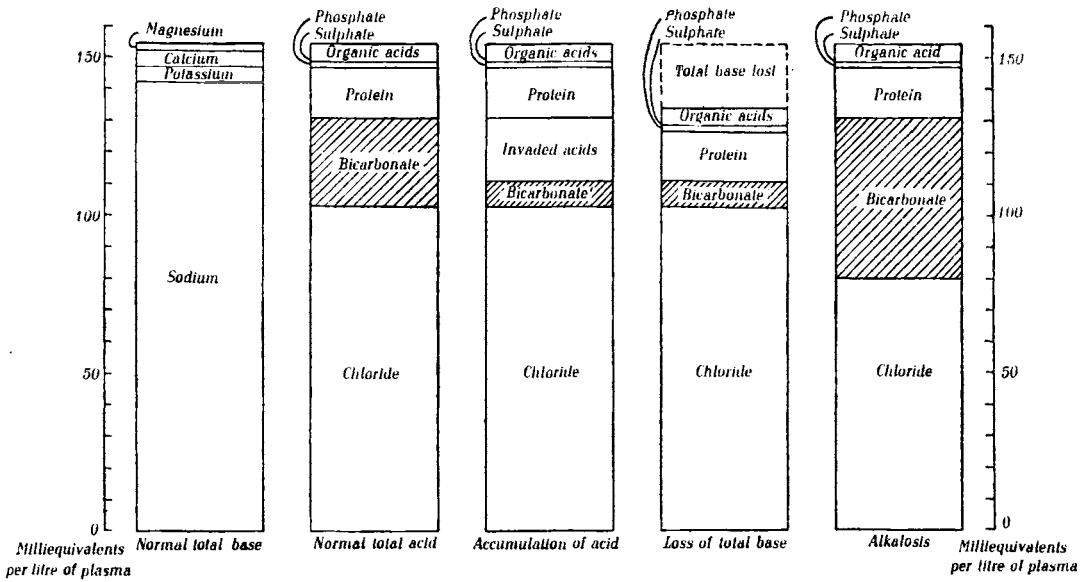

Fig. 1. The salt content of plasma under normal conditions, in acidosis and in alkalosis. The first two columns represent the normal salt content of plasma, the two following columns conditions in acidosis caused by accumulation of acid and loss of total base. The last column, finally ,indicates the anion content of plasma in alkalosis.

If the bicarbonate content of the plasma is reduced to 20–16 millimols the condition may be characterised as a *mild acidosis*. If the reduction is more considerable (16–10 millimols) the acidosis may be termed *moderate,* while with a reduction to below 10 millimols we have *severe acidosis*. Clinically bicarbonate values lower than 10 millimols are quite frequently encountered. So far the lowest value measured was observed by the author[102] in a child with diabetic coma in whom the bicarbonate content of the serum (the total carbon dioxide content) was reduced to 1.3 millimol, or about $^1/_{20}$ part of the normal value; the disease terminated with the child's recovery.

2. The Clinical Symptoms of Acidosis.

In milder (20–16) millimols) and moderate (16–10 millimols) acidosis in adults *the clinical symptoms are often uncharacteristic,* and further they are frequently masked by the primary disease, a fact which contributes much to render the diagnosis difficult. Our knowledge of the symptoms of acidosis is nevertheless quite considerable, because it has been possible through experimental research to furnish an important contribution to the clinical aspect of acidosis (see p. 152). Though the symptoms of the affection are less characteristic they are often very troublesome, and the demonstration of acidosis at a sick-bed has in numerous cases thrown light upon the picture of a disease which would otherwise merely be characterised by the terms »low general condition« and »increasing weakness«.

In the *milder degrees of acidosis* the patients frequently only complain of fatigue and indisposition and have little desire to be out of bed. In this stage there is, in addition, often a lack of appetite, besides nausea and headache. Not rarely the mental fatigue is pronounced in the form of a reduced power of concentration. Even the smallest efforts and decisions seem troublesome (e.g. shaving, reading the newspaper, dressing); the inclination for conversation is also frequently appreciably reduced. In *moderate acidosis* there is often dryness of the tongue, a symptom which, according to the author's[91] investigations, is much more characteristic of acidosis (and of paralytic ileus) than of de-

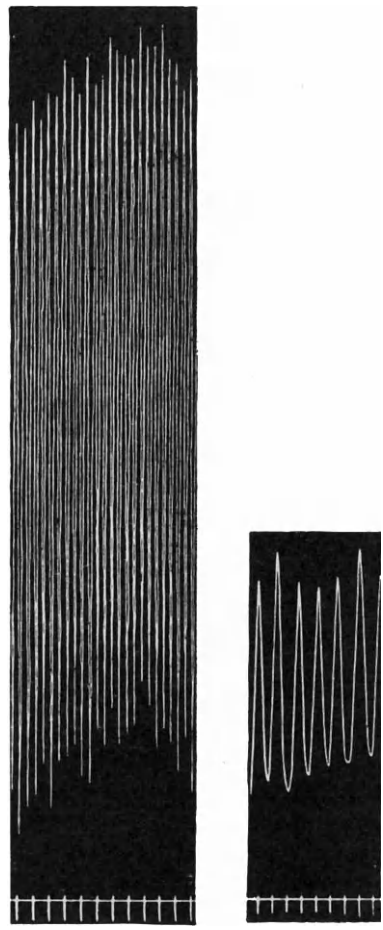

Fig. 2. Acidotic dyspnea.

Respiratory curve of a 46-year old patient with severe renal acidosis (plasma bicarbonate 5,2 millimols) caused by cystic kidneys (Case record No. 34). The curve to the right is from a normal individual. Time intervals 5 seconds.

From Means, J., and Rogers, O., Am. J. M. Sc., *153:* 420, 1917.

hydration. *Not until the bicarbonate content of the plasma has been reduced to half, i. e. to about 12–14 millimols, does the characteristic acidotic dyspnea occur.* At first only the depth of the respiration is affected, later also its frequency. The milder degrees of dyspnea are often overlooked by physicians and as a rule are only recognised by the patients as a dyspnea

on exertion. Following reduction of the bicarbonate content to between 10 and 7 millimols, i. e. in *severe acidosis,* pronounced dyspnea often develops, and both the depth and frequency of the respiration are greatly affected (see Fig. 2). There is violent airhunger and the respiration is often noisy, but the movements of the chest take place without difficulty. It is this form of dyspnea, Kussmaul's »grosse Athmung«, which has so impressed clinicians and has contributed to the early recognition of the fact that acid poisoning was present in diabetic coma and infantile diarrhea.

If consciousness is not affected to any great extent, the dyspnea is often felt by the patients to be unpleasant, though perhaps as a rule less distressing than might be expected from the dramatic clinical picture. The patients sometimes describe their condition as »a feeling as if they had just been running fast.« This was the expression used by the 46 year old negro with bilateral renal cysts whose respiration curve is reproduced in Fig. 2.

Following reduction of the bicarbonate concentration to below 10 millimols, consciousness will often be distinctly affected, but the author has repeatedly seen patients who were practically mentally normal though the bicarbonate value had been reduced to 8–9 millimols (see p. 88). The nature of the primary disease and the presence of other complications (especially infection and severe dehydration) will also frequently influence the state of consciousness. In the severest degrees of acidosis, vomiting, pains in the muscles, and loss of weight (caused, besides by dehydration, by destruction of the cells as a result of the acidosis) are common symptoms. Only when the bicarbonate value falls to below 6–7 millimols does *acidotic coma* with loss of consciousness almost regularly set in, though it may also occur at a considerably earlier stage.

The clinical symptoms of acidosis in children are generally much less conspicuous than in adults (Drucker[38], Kirk[97]). Thus it is not rare to see children sitting up in bed playing though the bicarbonate values of their plasma (4–5 millimols) would nearly always involve profound coma in adults.

In most cases of severe acidosis there will at the same time be symptoms of dehydration. Since this complication requires special consideration with respect to treatment, dehydration and its relation to acidosis will be discussed in a special section (see p. 24).

3. Causes of Acidosis.

The principal causes of acidosis are *accumulation of acids in the body and great losses of alkaline secretions.* Often both causes will contribute simultaneously to the development of the acidosis. As in diabetes, the increase of acid may be due to an abnormal *production of acid,* or it may, as is the case in renal insufficiency, be caused by *the retention of acid.* Finally *the introduction into the body of large amounts of acid,* as in hydrochloric acid and sulphuric acid poisoning, may give rise to a considerable degree of acidosis.

A vivid impression is gained of the many-sided nature of the acidosis problem when it is kept in mind that in certain forms of acidosis we are concerned with an accumulation of organic acids, in other cases with inorganic acids, and in others again with both organic and inorganic acids. Of the organic acids the keto-acids (β-hydroxybutyric acid and acetoacetic acid) and lactic acid are the most important, but it is highly probable that other organic acids too, the nature of which is not yet established, are involved in several forms of acidosis. A characteristic of the keto-acids is that they accumulate under conditions in which the carbohydrate combustion is affected, whether this be due to the fact that the organism, as in diabetes, cannot burn carbohydrate to its normal extent, or the cause is that owing to an insufficient supply there is not enough carbohydrate at disposal. The latter form of acidosis, hunger acidosis or inanition acidosis, occurs in a milder degree in numerous affections, in which the intake of nourishment is diminished.

Lactic acid acidosis, which may frequently reach considerable degrees, is seen under physiological conditions in hard muscular work and further in affections in which the intake of oxygen is insufficient (anoxemia), that is to say, especially in cardiac decompensation and circulatory insufficiency.

Of the inorganic acids sulphuric acid and phosphoric acid are of special interest, the sulphate ion and phosphate ion being retained in an early stage when the kidneys are injured; both these ions are constantly being formed in the organism during the normal protein metabolism. As the chloride ion is more easily excreted, hydrochloric acid will chiefly be of importance in hydrochloric acid poisoning and in a therapeutic administration of large amounts of ammonium

chloride and calcium chloride which after resorption from the intestine have the effect of hydrochloric acid (see p. 152).

With the loss of sodium bicarbonate from the body its concentration in the plasma will decrease and an acidosis will arise. Large losses of alkaline secretions chiefly occur in severe diarrheas and with long-lasting intestinal and bile fistulas. It is important to note that not only will the loss of sodium bicarbonate be able to produce acidosis, but also the loss of sodium and potassium in other compounds than in the form of bicarbonate. This will appear from Fig. 1 in which the two columns in the left half of the figure show the normal salt content of the plasma. The total content of sodium, potassium, calcium, and magnesium is given in the first column and is called the *total base**). The acid elements (among these bicarbonate, which, as already stated, is a weak acid) are entered in the next column and are termed the *total acid*. The figure shows that the sum total of the basic and acid elements is the same; this is understandable as the degree of acidity of the plasma only deviates inconsiderably from the neutral point. With greater losses of sodium and potassium the total base column will be lower. Since the two columns, »total base« and »total acid« must necessarily be of equal height if no violent changes in the degree of acidity of the plasma are to set in, a diminution of the total base column will involve a corresponding compression of

*) The term total base as an expression for the total content of sodium, potassium, calcium and magnesium in the plasma is an important quantity in biochemistry, especially in investigations concerning the electrolyte metabolism. The normal total base concentration in the plasma and serum is c. 155 milliequivalents. The importance of determining the total base is due amongst other things to the fact that technically it is possible to determine the value by a single analysis, while there exists no method for determining the total amount of acid. The determination of the total base further represents the only method for a quantitative determination of the organic acids in the plasma, these being calculated by subtracting the determinable acid constituents (chloride, bicarbonate, sulphate, phosphate and protein) from the total base value, a fact which is of great importance in acidosis investigations. The term itself, total base, is however hardly a good choice, since experience has shown that it gives rise to confusion with the term alkali reserve, which, as previously stated, denotes something quite different, viz. the bicarbonate content of the plasma. The term total base has however become so firmly rooted in American and English literature that at present it is hardly possible to alter it, even though the term total cation concentration would be preferable.

the total acid column. *This will not rarely in a particular degree affect the bicarbonate, the amount of which may quickly be regulated by the removal of carbon dioxide through the lungs* (see the column »loss of total base« in Fig. 1). *A reduction of the total base value in the plasma will therefore often involve a diminution of the bicarbonate value or, in other words, will cause acidosis.*

4. The Neutrality Regulation of the Organism.

In addition to *bicarbonate, the hemoglobin* in the blood, and *the proteins* and *phosphates* of the plasma and tissue fluids are of significance in the neutralisation of invading or abnormally accumulated acids in the body. The total neutralising capacity is so great that it is possible to administer 1 litre 1 normal (3.5 p.c.) hydrochloric acid to an adult human subject without a fatal outcome. Only about 60 p.c. of the amount of acid administered will be neutralised by bicarbonate, but the special significance of this substance is that its amount can be changed almost momentarily, and that the decomposition product carbon dioxide can leave the organism through the lungs. After the removal of invading acids by excretion or combustion, or after restoration of the normal total base content in the plasma (e.g. by saline injections) the bicarbonate content of the plasma will rapidly become normal again, since carbon dioxide is constantly produced by combustion in the tissues and instantly combines with any total base available to bicarbonate.

Of other neutrality-regulating factors we may mention *the direct secretion of acids into the urine,* that is to say the excretion of a strongly acid urine, and *the secretion of acids in connection with alkaline salts* (sodium and potassium) *and in connection with ammonia.* As there is a limit to how sour a urine the kidneys can produce, the removal of the acids as alkaline and ammonia salts is of far greater importance than the excretion of the free acids. By excretion of the acids as alkaline salts the organism suffers a loss of salt (total base loss) which in severe cases of acidosis may become considerable, whereas the neutralisation by means of ammonia occurs without loss of total base. The production of ammonia takes place exclusively in the kidneys. The production in 24 hours may in severe cases of acidosis mount from a normal

value of c. 0.5 g to 5—10 g*). In renal diseases or renal injuries the production of ammonia, however, often fails.

In those instances in which the acidosis is due to the presence of organic acids, *a combustion of these acids*, which in the case of keto-acids takes place under the influence of insulin, will be an important factor in the neutrality regulation of the organism. As a result of the combustion carbon dioxide is formed, which at once as bicarbonate takes the place of the organic acids. As far as lactic acid is concerned, a further removal is possible through transformation into glycogen.

5. Review of the Clinical Forms of Acidosis.

As the clinical diagnosis of acidosis is often uncertain or impossible on account of the uncharacteristic symptoms, it is, as was pointed out in the preface, of great importance to know in which affections and under what circumstances we may expect to find acidosis. In these pathological states, determination of the bicarbonate in the plasma is highly advisable, for apart from the severe cases of acidosis with typical Kussmaul respiration this analysis frequently represents the only possibility of making a diagnosis. For the sake of clarity Table 1 gives a list of the chief clinical forms of acidosis; the separate groups will in later sections be made the subject of a thorough discussion. The Table conveys a good impression of how widespread acidosis is as a complication of medical and surgical affections.

*) On account of the simple technique determination of the ammonia in the urine has been much used in clinics for the demonstration of acidosis, and is still in Danish hospitals the most frequently employed laboratory analysis for the diagnosis of acidosis. The method is chiefly of value in diabetes, since the determination often fails in renal forms of acidosis, the production of ammonia in the kidneys being frequently much reduced in renal insufficiency. In the presence of infection of the urinary system, with bacterial decomposition of the urea, the determination is directly misleading. Even in the treatment of diabetes the ammonia analysis hardly, in the author's opinion, yields much more than the qualitative determination of the keton bodies in the diagnosis of incipient acidosis, and in precomatose diabetic cases it is of much less value than the determination of the bicarbonate in the plasma. For this reason the author has discontinued the determination in his hospital department and has not felt the loss of it.

Table 1.
Survey of clinical forms of acidosis.

1. *Physiological acidosis*
   Lactic acid acidosis during hard physical work
2. *Acidosis due to uncomplicated loss of alkali*
   Fistula of the small intestine
   Bile duct fistula
   Bile drainage
   Pancreatic fistula
3. *Acidosis caused by loss of alkali complicated by infection and intoxication*
   Cholera
   Other severe diarrheas in adults (dysentery, meat poisoning, fungal poisoning)
   Acute gastroenteritis in children
4. *Acidosis due to persistent anacid vomiting*
   Hyperemesis gravidarum
   Anorexia nervosa
5. *Acidosis caused by an abnormal production of acid*
   Diabetes mellitus
   Ketonemic vomiting in children
   Inanition acidosis
   Acidosis in anoxemic conditions (cardiac decompensation, insufficiency of the peripheral circulation, shock, severe anemias)
   Acidosis in anesthesia
6. *Acidosis as a consequence of an inhibition of the tissue oxidation (inhibition of the intermediary metabolism)*
   Lactic acid acidosis in guanidine intoxication
7. *Acidosis due to retention of acid (and loss of total base)*
   Acute nephritis
   Mercuric chloride poisoning
   Eclampsia of pregnancy
   Chronic nephritis
   Renal amyloidosis
   Hypertrophy of the prostate
   Other surgical urinary diseases
8. *Acidosis due to an abnormal intake of acid*
   Sulphuric acid and hydrochloric acid poisoning
   Medicinal acidosis (following administration of calcium chloride and ammonium chloride)
9. *Acidosis in various other intoxications*
   Salicylic acid poisoning
   Methylsalicylate poisoning
   Aspirine poisoning
   Methyl alcohol poisoning
   Methyl chloride poisoning

10. *Other forms of acidosis not yet fully elucidated*
    Liver insufficiency
    Acute febrile bile duct and liver affections
    Acidosis in thyreotoxicosis
    Acidosis in acute suppurative otitis media in infants
    Acidosis in other severe infectious diseases and in septic conditions
11. *Premortal acidosis*
12. *Chronic acidosis*
    Renal rickets
    Renal osteomalacia
    Osteomalacia following prolonged ingestion of acidotic drugs
    Osteoporosis in long-lasting hepatic fistulas

The share of the acidosis in the pathological picture and its bearing on the prognosis is very different in the different diseases. In diabetic coma acidosis is often the main symptom, on the treatment of which the patient's fate depends, while the final prognosis in chronic progressive nephritis is as a rule independent of whether or not there is acidosis. In acute gastroenteritis in children and in prostatic hypertrophy acidosis occasionally occurs as a grave complication, the treatment of which may be decisive for the recovery of the patient.

Acidosis is seen in its purest form in fistulas of the small intestine, and in hepatic drainage where the case is not complicated by infection, peritoneal affections or severe dehydration, while the pathological picture in infantile diarrhea and in cholera in adults is often overshadowed by the infection present. In uremia, finally, the picture will often be strongly influenced by the uremic intoxication and cardiac symptoms.

6. Complications of Acidosis: Dehydration, Salt Deficiency, and Uremia.

Even though acidosis is a complication in itself and does not occur as an independent disease, it will so frequently be accompanied by other complications that these require mention here. The most important are dehydration, loss of salt, and uremia, which often in no small degree affect the clinical picture and will frequently necessitate special treatment. An understanding of the nature of these complications

and their relation to the acidosis will often contribute to the understanding of vague pathological conditions[98].

a. *Dehydration and loss of salt.* For the understanding of the dehydration problem it is important to realise that water is chiefly retained in the body in combination with salt, and that loss of salt and fluid in general occurs simultaneously (e. g. in vomiting and diarrhea). In dehydration a low salt content (total base content) will therefore often be found in the plasma, and by determining the total base value it is possible to form an estimate of the degree of dehydration. The normal total base concentration in the plasma is about 155 milliequivalents; in heavier losses of salt the value may be reduced to 130 milliequivalents.

It was stated above that a loss of total base will usually be equivalent to dehydration. Since a total base reduction will also, as was explained on p. 21, automatically involve a reduction of the bicarbonate concentration of the plasma, the close connection between dehydration and acidosis will be understood*). The acidotic condition, on the other hand, will often contribute to aggravate the dehydration. Thus in diabetes large amounts of sodium and potassium (total base) are frequently lost in connection with the excretion of keto-acids.

The clinical symptoms accompanying dehydration are rather vague in the mild and moderate cases so that, as in acidosis, it is often impossible to make a diagnosis with an ordinary clinical examination. In the author's experience the symptoms are usually far less troublesome than in corresponding degrees of acidosis, though they bear a certain resemblance to the acidotic symptoms. In mild and moderate degrees of dehydration physical and mental fatigue, loss of appetite, nausea, and oliguria are observed. In this connection it may be mentioned that the condition of the tongue affords no clue to the diagnosis, for patients with a normal salt content of the plasma may have a dry tongue, while conversely, patients with a fairly considerable dehydration may have a moist tongue (Kirk[91]). Only in severer cases of salt deficiency and

*) Upon the loss of acid secretions (e. g. vomiting of acid stomach-contents), on the other hand, the effect on the bicarbonate concentration of the plasma will be different; bicarbonate ions in the plasma will replace the chloride ions lost in the vomitings (see Fig. 1); the result then will be a rise in the bicarbonate value of the plasma, i. e. an alkalosis.

dehydration does the characteristic picture of desiccation appear. The face becomes haggard, the eyes sunken, and the turgidity of the skin is reduced. Frequently cramps of the calves occur, the voice gets weak and aphonic, and the mucous membranes of the eyes dry, while the tension of the eyes decreases. Finally symptoms of shock set in; the blood pressure falls, the extremities grow cold, and there is cyanosis and coma.

The injurious effect of dehydration often manifests itself in a rise in the value of the blood urea caused by an abnormal tissue cell destruction; as pointed out below, the rise in blood urea may also be caused by the oliguria present. On examination of the blood, the findings are, in addition to a reduced total base value, a reduced water content of the plasma and a corresponding increase of the plasma protein value and of the erythrocyte number per cmm.

The treatment of salt deficiency and dehydration[98] consists in the administration of an isotonic (physiological) sodium chloride solution or (and) an isotonic sodium bicarbonate solution, depending on whether the analysis has shown a reduction of the plasma chloride*) or (and) plasma bicarbonate value. Both solutions may under suitable circumstances combat the loss of salt and dehydration, the isotonic sodium bicarbonate solution is, *in addition,* able to relieve the acidosis.

b. *Uremia.* Of the clinical symptoms present in dehydration oliguria deserves a somewhat fuller discussion, for with a considerable reduction of the diuresis, retention of urinary components in the blood may occur, or in other words, *uremia may arise as a result of loss of salt and dehydration.* It is of great importance to distinguish this form of uremia from that caused by renal disease. In dehydration the kidneys themselves are not affected, apart from a possible lighter injury as a result of the universal effect of the dehydration on the cells of the body. Despite the fact that the renal function is reduced, *the functional capacity* in the widest sense is not affected, nor can any symptoms of renal disease be demonstrated in the cases in which the patient is cured of his primary disease. *In uremia caused by dehydration,*

*) The normal plasma chloride concentration is 100-110 millimols (or milliequivalents) per litre. In cases of severe salt deficiency a reduction to 70-75 millimols may be seen.

therefore, the prognosis is good if the loss of salt and dehydration can be relieved. It is important, however, that this treatment should be carried out as quickly and as consistently as possible, since the uremia in itself may constitute a danger to life owing to the intoxication. Sometimes a vicious circle may arise, the uremic condition involving further vomiting, which will exacerbate the loss of salt and the dehydration.

Acidosis too, (i. e. without severe dehydration or oliguria) *may frequently cause the development of uremia.* The often very considerable rise in the blood urea in acidosis must be regarded as indicative of an increased destruction of tissue protein. It is the author's impression that the injury to the tissues is much greater in acidosis than in a corresponding degree of uncomplicated dehydration. The rapid improvement of the uremia that often follows the treatment of acidosis with isotonic sodium bicarbonate solution must no doubt be regarded as a consequence of a reduction or cessation of the tissue cell destruction. *In uremia caused by acidosis the prognosis is on the whole fairly good if the acidosis is relieved by effective treatment.*

In some cases of acidosis *a direct kidney lesion* undoubtedly also occurs. Thus in diabetic coma albuminuria and pronounced cylindruria are often observed; in this disease, especially, the uremia is frequently grave (Warburg[225]).

Since dehydration is such a frequent complication of severe acidosis, both forms of uremia may be found simultaneously. Common to both forms is, as already mentioned, the relatively good prognosis, with correct treatment. In renal disease, be it noted, both dehydration and acidosis may contribute to aggravate a uremia of renal origin.

To sum up we shall finally emphasise that in acidosis three different forms of uremia may occur: 1) uremia caused by the acidosis, 2) uremia caused by dehydration, and 3) uremia caused by renal disease (renal uremia). The forms of uremia may occur singly, two together, or all three simultaneously. In the renal form of uremia the prognosis is usually bad, in the other two forms it is fairly good provided the correct therapy is instituted in time.

II

The Treatment of Acidosis

For the lines on which acidosis should be treated the following main rules may be laid down: *In the treatment of non-diabetic acidosis the administration of an isotonic (1.3 p.c.) sodium bicarbonate solution is the chief remedy. In diabetic acidosis insulin therapy is the specific means for relieving the acidosis, but the use of an isotonic sodium bicarbonate solution is advisable as a supplementary treatment in severe comatose cases. Finally, in diseases in which the supply of nourishment has been compromised and an inanition acidosis may be supposed to be present, administration of glucose is required as the sole or as a supplementary acidosis therapy.*

A. Treatment with an Isotonic, 1.3 p.c., Solution of Sodium Bicarbonate.

1. Indications.

Treatment with an isotonic solution of sodium bicarbonate will usually be indicated in non-diabetic acidosis with a reduction in the bicarbonate of the plasma to below 19–16 millimols. The field of application, however, not only comprises cases of non-diabetic acidosis but also such forms of diabetic coma in which insulin treatment does not quickly bring about the desired improvement, or where the condition of the patient is so dangerous that the rapid supervention of death is to be feared (Kirk[93], 1938). Even if the patient is almost moribund the practitioner should not hesitate to institute the first treatment in the patient's home. A more detailed account

of the indications and course of alkali treatment in diabetic coma will be given on p. 97. Owing to the frequency of diabetic coma this disease constitutes one of the main fields for bicarbonate treatment.

In more pronounced cardiac insufficiency as well as in forms of shock with clinical signs of capillary injury, intravenous administration of alkali is usually contra-indicated, since the treatment in such cases may cause peripheral edemas and pulmonary edema. The same objection possibly applies to glomerular nephritis in the first stages of the affection, but the clinical data concerning the treatment of acidosis in this disease are as yet very sparse.

2. *Forms of Administration.*

The isotonic solution af sodium bicarbonate can be administered intravenously, intrasternally, subcutaneously or rectally. Since the clinical conditions in which bicarbonate treatment is adopted as a rule necessitate a rapid relief of the acidosis, intravenous administration will usually be employed; in babies, however, the administration will most frequently be subcutaneous. Rectally bicarbonate may be given as a 5. p.c. solution, and can usually be replaced by ingestion of bicarbonate and liquid by mouth. *As a main rule for the administration of bicarbonate it applies that while the solution for subcutaneous use must be absolutely sterile, it is sufficient for intravenous injection to use solutions of the best quality of sodium bicarbonate in sterile water, without any special sterilisation of the powder employed.* Incidentally it should be noted that in subcutaneous injection of isotonic sodium bicarbonate solutions the author has never observed cases of local irritation, while such have been described in the literature after subcutaneous injection of concentrated bicarbonate solutions.

3. *The Preparation of Isotonic Sodium Bicarbonate Solutions.*

Isotonic solutions of sodium bicarbonate for clinical use can be prepared in different ways (by direct solution, Seitz-filtering, autoclaving). *To all these solutions it applies that they do not tolerate sterilisation by heating unless it takes place in sealed or hermetically closed containers,* for on being heated the bicarbonate gives off carbon dioxide and is trans-

formed into the highly alkaline carbonate. Sterilisation in an autoclave in flasks closed with a cotton plug therefore must not take place.

In practice the following solutions may be used.

1) A solution made by dissolving 13 g of sodium bicarbonate (the sodium bicarbonate of the pharmacopeia or a similar one of the best quality) in one litre of sterile water. Immediately before use a 13 g powder is dissolved in a flask containing 630 c.c. of sterile water, which is then made up with boiling water to 1 litre. The advantage of this method is its simplicity, as no more elaborate preparations are required than for a saline injection. In hospital departments where patients with acidosis are frequently received, it is convenient to have a store of such 13 g powders ready weighed. As the solution is not absolutely sterile, it should not be used for subcutaneous injection.

2) Sodium bicarbonate solution sterilised by autoclaving in sealed or carefully closed containers.

Methods of sterilising bicarbonate solutions by autoclaving have been devised by several authors, thus already by Sellards[197, 198] in 1911. From more recent years there are devices by Holmes and Cullen[74] (1938) and by Aalkjær and Nielsen[149, 2] (1938).

Aalkjær and Nielsen recommend the following procedure. Patent bottles containing ½ litre made by Kastrup Glassworks, Denmark, are used. The bottles are filled with 450 c.c. of 1.3 p.c. sodium bicarbonate solution and placed upside down in the autoclave. This precaution is taken to ensure the tightness of the closure, as the contents are liable to run out, partly or entirely, if the closure is not perfectly tight. They are heated for half an hour to 100°, after which the temperature is raised to 120°. After an hour's heating at this temperature they are cooled slowly so as to avoid breaking of the bottles. As a rule the autoclave should not be opened until 2-3 hours after the autoclaving has been completed.

Sterilisation by autoclaving has for many years proved practicable but it is principally suited for larger hospital departments. The flasks used for the sterilisation should be of the best quality resistent glass so as to avoid turbidity of the fluid owing to the separation of silicate from the glass. The solution can be used both for intravenous and for subcutaneous injections. The sterilisation method requires the

greatest care and should only be entrusted to particularly reliable persons, for if the flasks are imperfectly closed a transformation of bicarbonate to the highly alkaline carbonate will take place.

The sterilisation method devised by Nielsen was used in the preparation of Sol. natrii bicarbonatis isotonica Pharmacopoea Danica ed. VIII (Supplement 1941).

The following three preparations have been placed on the market at my request by the chemical factory »Løven«, Copenhagen.

3) Sol. natrii bicarbonatis 8 p.c. Leo, in bottles containing 162.5 c.c. of solution or 13 g of sodium bicarbonate.

This solution, like the two succeeding ones, is made by filtering through a Seitz filter and is thus sterile. After dilution of the contents of the bottle with sterile water to 1 litre it can be used both for intravenous and for subcutaneous injection.

4) Sol. natrii bicarbonatis 1.3 p.c. Leo, in bottles containing 150 c.c. The solution is intended for the treatment of infants and is ready for use after the bottle has been heated in water.

5) Sol. natrii bicarbonatis 1.3 p.c. Leo, in 1 litre resistent glass ampoules with two necks.

The ampoule is intended for general practitioners for treatment in the home in such cases of diabetic coma in which the condition is so dangerous that a rapid fatal outcome is to be feared, so that the treatment cannot be postponed until after admission to a hospital.

Before use the ampoule is heated by immersing in warm water, or warm water is poured over it. Then the lower neck is filed off the ampoule, and a rubber tube about 9 mm in diameter and with walls 2 mm thick and at least 30 cm long with stop cock and needle is fitted on to the filed off point of the ampoule. After the upper neck of the ampoule has been filed off the apparatus is ready for use.

4. Dosage of Sodium Bicarbonate.

The quantities of bicarbonate to be administered in each case in order to relieve the acidosis can be calculated approximately by means of a nomogram constructed by Van Slyke[216] (Fig. 3). The nomogram is based on the observation that to

attain a rise of 1 millimol of bicarbonate, the administration of 0.06 g of sodium bicarbonate per kg body weight is required, a numerical proportion which may also be used for calculating the dosage[158]. If the cause of the acidosis persists, it will of course be necessary to administer larger amounts of bicarbonate than indicated by the nomogram, but the use of the latter affords security against over-dosing (and the risk of alkalosis and tetany). It is not necessary, however, to administer so much bicarbonate at the first treatment that the plasma value becomes normal, *the decisive thing being to raise the bicarbonate value as quickly as possible above the limit which conditions the difference between coma and clear consciousness.* This means, in practice, that at the first treatment it should at any rate be attempted to raise the bicarbonate content to 12–14 millimols. Usually 1–2 litres of isotonic sodium bicarbonate solution will be given at the first sitting. *In dangerous cases, under circumstances where there is no possibility of making a plasma bicarbonate analysis, up to 2 litres of isotonic sodium bicarbonate solution may without hesitation be administered intravenously, without any risk of overdosing*[100]. This dose will in fact often be sufficient to relieve the coma.

During the further treatment the dosage will depend on whether the acidosis recurs continually or whether its cause is removed (e.g. by operative closing of an intestinal fistula, cessation of diarrheas etc.). During the first days it will often be desirable to check the bicarbonate value of the plasma several times daily and adjust the dosage to the analytical results. This applies especially to diabetic coma in which a continued excessive formation of keto-acids may cause a reproduction of the acidosis, while a rapid combustion of these acids under the action of insulin will result in a greater rise in the bicarbonate content of the plasma than corresponds to the amount of bicarbonate administered.

5. Therapeutic Technique.

The intravenous injection of the bicarbonate solution is best carried out by means of a Gram transfusion apparatus with an infusion needle. If the patient's veins allow it, a cannula of large calibre should be chosen (1.2 mm external diameter) perhaps furnished with a transverse attachment for support during the injection. If no cardiac complications

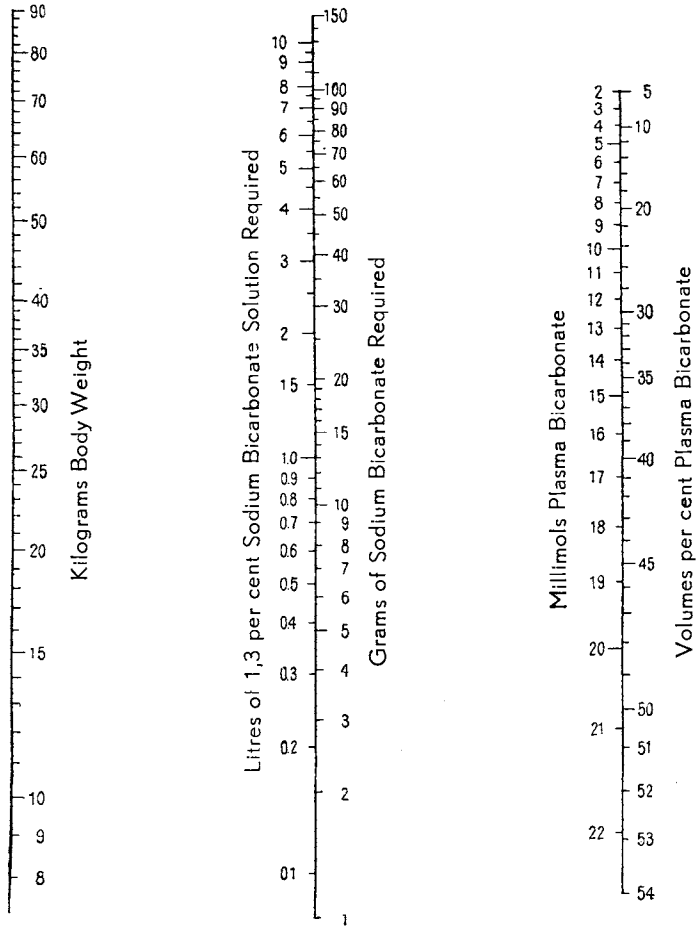

Fig. 3. Nomogram for calculating the amount of sodium bicarbonate required in conditions of acidosis to raise the bicarbonate content of the plasma to 25 millimols per litre (or 60 volumes per cent). A straight line cutting the scales for body weight and plasma bicarbonate will cut the middle scale at a point indicating the bicarbonate administration required.
After Van Slyke, D., »Acidosis and alkalosis«.
Bull. New York Acad. Med., *10:* 103, 1934.

are present, the injection may without risk be made at a rate of 1 litre per 10–15 minutes.

In cases where the subcutaneous veins are poorly developed the injection may be given intrasternally.

In infants the injection is usually given subcutaneously on the chest, the back, or the outer side of the thighs, with a 50 c.c. syringe with an excentric point for the needle. The skin is disinfected with a 2 p.c. alcoholic iodine solution, after which 50–100 c.c. are injected at each place with a long thin needle. The place of insertion is closed with cotton and collodion. In particularly dangerous cases the solution may be injected slowly into the sagittal sinus.

6. Special Precautions in the Treatment of Renal Acidosis.

In cases where there is a renal acidosis, 1–2 g of calcium chloride or calcium gluconate should be added to each litre of sodium bicarbonate solution. This precaution is taken because the plasma in uremia, owing to the retention of phosphate in the blood, often has low calcium values. The reduced calcium values, however, do not usually give rise to tetany, for under the influence of the acidosis the calcium in the plasma is more highly ionised than usual. By the administration of bicarbonate, however, the ionisation is reduced, so tetany often occurs during the injection even though there is no overdosing with bicarbonate. By the addition of calcium chloride or calcium gluconate this secondary effect may usually be avoided.

In acidosis due to loss of alkali in diarrheas (acute gastroenteritis) the addition of calcium may likewise be recommended, for simultaneously with the loss of alkali, a considerable amount of calcium is frequently lost in the watery stools.

7. The Treatment of Acidosis with Bicarbonate Powders and Tablets.

Oral ingestion of bicarbonate is chiefly indicated in affections where there is a tendency to slow development of the acidosis, thus especially in chronic renal diseases and as an after-treatment in severe cases of acidosis. For this treatment either bicarbonate powders or bicarbonate tablets (Trochisci natrii bicarbonat.) may be used. A level teaspoonful of sodium bicarbonate weighs 4–5 g.

8. Effect of the Administration of Bicarbonate.

The effect of the administration of alkali in severe acidosis is frequently dramatic, for it is not rarely seen that deeply

comatose patients recover from their comatose condition during the intravenous injection. Even in cases in which the patients are almost moribund, the treatment may sometimes be effective. It is therefore beyond doubt that it may in several cases be life-saving.

The result of the bicarbonate injection in cases of acidotic coma is usually first observed by *the return of consciousness.* The patient opens his eyes, begins to talk of his own accord, or answers questions put to him. Often consciousness is restored after the administration of 500–700 c.c. of fluid presumably because the bicarbonate solution, by direct introduction into the blood stream, causes a rapid change in the degree of acidity in the centres of the central nervous system. It is characteristic of acidotic coma (as of most other forms of coma) that restitution of the normal mentality upon cessation of the coma occurs with astonishing rapidity and that no mental defects are later observed; so it must be supposed that the coma does not cause any considerable organic injury to the brain. After the recovery of consciousness *the respiration* will as a rule during the continued treatment with alkali grow less deep and stertorous, the character of »grosse Athmung« disappears but the increased respiration frequency, according to the author's observations, usually persists for several hours or even for a day and night after the relief of the acidosis. With the treatment of the dehydration the shock symptoms will often appreciably decrease, the blood pressure will rise, the pulse become fuller, the expression more natural, and the skin warm and moist. After cessation of treatment the patient's frame of mind is often definitely euphoric. Not rarely a considerable diuresis sets in at this juncture, even occasionally where there has previously been a prolonged anuria (see p. 57, Fig. 6).

The as a rule excellent immediate effect of the treatment of acidosis with an isotonic sodium bicarbonate solution is probably due to the fact that it is thus possible, within quite a short time, to relieve or mitigate both the acidosis, the salt deficiency, and the dehydration.

The lasting results of the bicarbonate treatment will depend on the nature of the primary disease and the possibilities of avoiding a recurrence of the acidosis. In intestinal fistulas and hepatic drainage, where it is possible to prevent a continued loss of alkali by a surgical operation, the effect of the treatment will be permanent. In several cases of sur-

gical renal acidosis, especially with hypertrophy of the prostate, the treatment also seems capable of producing a lasting cure of the acidosis, as the latter does not recur after the administration of alkali is discontinued. In uremia as a result of chronic progressive nephritis the treatment is as a rule merely symptomatic.

9. Secondary Effects of the Treatment. Overdosing.

In addition to the above-mentioned cases of convulsions in bicarbonate treatment of renal acidosis, other secondary effects are occasionally observed as a result of alkali therapy. Thus when the solution runs in very quickly, a feeling of oppression may occur in rare cases. The occurrence of chills immediately after the treatment, according to the author's experience, is due to the use of water of defective quality; hence the use of *freshly* distilled water*) or, failing this freshly boiled tap-water is recommended for the preparation of the bicarbonate solution. The use of distilled water left for a long time in an unsterile condition is probably the most frequent cause of secondary effects in the intravenous administration of saline solutions.

The earlier literature has a number of reports of the occurrence of convulsions during injection of sodium bicarbonate and sodium carbonate solutions in non-renal forms of acidosis, as also of the observation of hyperemia of the meninges and small hemorrhages of the brain found at the post-mortem examination. It must be supposed that these effects are due to the injection of strongly hypertonic solutions as well as the administration of several hundred grams of sodium bicarbonate within a short time.

Overdosing with sodium bicarbonate will raise the bicarbonate concentration of the plasma above the normal value (alkalosis) with the possibility of alkalotic tetany setting in (see p. 41). The occurrence of severe alkalosis as a result of overdosing has especially been observed in renal diseases, in which the kidneys, owing to reduced function, are unable to excrete an excess of bicarbonate.

*) In preparing distilled water for intravenous use the prescriptions given in the Pharmacopoea Danica VIII ed. for the preparation of Aqua destillata sterilisata may be recommended.

B. The Use of Other Alkaline Solutions for the Treatment of Acidosis.

As already stated, besides sodium bicarbonate solutions, sodium carbonate solutions were previously largely used for the relief of acidosis, in the main on the assumption that the acid-binding capacity of this substance is about 1.6 times as great as that of bicarbonate. The use of sodium carbonate solutions has, however, now been abandoned owing to the strong alkaline reaction of these solutions, their irritating local effect, and their tendency to produce hemolysis. In contrast with this, the use of sodium lactate solutions has been fairly widely adopted in American pediatry since 1930 under the influence of Hartmann[70] in St. Louis. There can hardly be any doubt that we have also in sodium lactate a rational means of combating acidosis, the lactate being converted in the organism into carbon dioxide and water. The carbon dioxide thus produced immediately combines with sodium to form sodium bicarbonate, *so that the final result will be the same as with the administration of bicarbonate.* It should be noted, however, that Hartmann uses racemic sodium lactate of which only half, namely the dextrorotatory form, d-lactate, undergoes combustion, as mentioned above, while the sinistrorotatory form is presumed to be transformed into glycogen. The recorded results of the sodium lactate treatment do not leave any doubt that with the administration of lactate a safe and considerable increase in the bicarbonate content of the plasma will usually be gained. The advantages of this therapy over the administration of sodium bicarbonate are stated by Hartmann and his coworkers to be the better keeping quality and the easier administration of the lactate solution. In the author's opinion there is no real advantage, since there is no great difficulty in making, keeping, and administering bicarbonate solutions. To this must be added that bicarbonate solutions for intravenous use can be made in no time by dissolving so common a substance as sodium bicarbonate in boiled water. Against the use of sodium lactate instead of sodium bicarbonate is the fact that the effect of the lactate is delayed, seeing that the combustion of the lactate administered does not come to an end until after about two hours. An additional, particularly weighty objection is that, even though this combustion is usually known to take place, *we have no guarantee that the organism in very exhausted, anoxemic or moribund patients will be able to metabolise lactate.* Hartmann himself seems to realise this, for in a survey of the treatment of acidosis in infantile diarrhea he says about cases in which the lactate therapy has been ineffective: »Perhaps such cases could be better treated with at least an initial dose of sodium bicarbonate,« and he adds, »In such infants failure to respond to sodium lactate therapy might be due ... to liver dam-

age and derangement of lactic acid metabolism.« For the same reasons the author, without having any personal experience of lactate treatment, prefers the therapy with isotonic sodium bicarbonate solution. Cullen[32], too, in the main shares this point of view (1936). In spite of the above statement, it must however be held that the lactate therapy introduced by Hartmann has been of the greatest importance for the combating of acidosis in American pediatry. The results gained by Hartmann will indeed be repeatedly discussed in the sequel.

C. The Treatment of Acidosis with Glucose Solution.

As stated in the introduction, parenteral administration of glucose solution is chiefly employed in *inanition acidosis.* However, in the opinion of many clinicians the administration of glucose is also valuable in the treatment of *diabetic coma,* as a supplement to insulin treatment. In *uremia in surgical and medical renal diseases* too, an indubitably favourable effect of glucose treatment is frequently seen, and occasionally even the recovery of consciousness. In many of these cases there is probably an inanition acidosis besides the actual renal acidosis, since the supply of nourishment, owing to nausea and vomiting, has often been poor for several weeks before the coma sets in. Not rarely the favourable effect of the treatment manifests itself in a decrease in the uremia. This reduction of the blood urea value may be a consequence of the diuretic influence of the sugar but is presumably chiefly due to a reduced tissue cell destruction.

If the glucose solution is administered subcutaneously, it is necessary that it should be isotonic, for which a 5 p. c. solution is used. If, on the other hand, the glucose is administered intravenously, a 20 p. c. concentration may be employed without risk, for the hypertonia will be balanced by the burning of the sugar. With the use of the isotonic solution the dose per sitting will as a rule be 1 litre; for the further treatment in inanition acidosis the presence of ketonuria will be a guide to dosing. In diabetic coma those cases in which the acidosis is considerable and the blood sugar value low will be particularly suitable for a glucose therapy, since a better insulin effect will be obtained by it and the possibility of a higher dosage of insulin.

D. Remarks on the Treatment of Acidosis with Physiological, 0.9 p.c., Sodium Chloride Solution.

Since acidosis, as stated on p. 25, will often entail a considerable loss of sodium chloride (when there is diarrhea, vomiting etc.), which manifests itself in a reduction of the plasma chloride value, the administration of physiological sodium chloride solution is often indicated. The amount of saline to be administered depends on the degree of loss; as a rule 1 or 2 litres a day will be sufficient, but in severe cases of dehydration (e. g. in cholera) the doses (even with simultaneous administration of isotonic bicarbonate solution) must often be increased to 5–10 litres. The treatment should be continued until the chloride value of the plasma has become normal.

Since saline therapy is so widely employed and valuable a form of treatment in hospital departments, *a more precise description of the role of this therapy in combating acidosis will be necessary*[95, 96].

In view of the fact that in cases of acidosis it is desirable that an approximately normal composition of the plasma and tissue fluids should be restored as quickly as possible, there can hardly be any doubt that, as stated above, a reasonable administration of saline is indicated when a great loss of sodium chloride has taken place. *For the treatment of the acidosis itself (the bicarbonate reduction), the administration of salt water is, however of far less value than the administration of bicarbonate. The saline will in the first instance only relieve the loss of salt and the dehydration, whereas the isotonic sodium bicarbonate solution will promptly relieve both the acidosis, the loss of salt, and the dehydration.* This is not rarely to be observed in practice, when often the condition of the patient is not appreciably altered by the administration of saline, but is improved following a bicarbonate treatment instituted afterwards (see e. g. p. 45). Upon the sudden administration of large amounts of saline the acidosis may even be seen to be temporarily aggravated, the amount of bicarbonate in the body being diluted and the concentration in the plasma reduced.

It must be admitted, however, that *in the long run* a saline therapy may bring about a real improvement in the acidosis. This is possible because, of the sodium chloride administered,

the kidneys selectively excrete the chloride while the sodium is retained and immediately combines with carbon dioxide from the combustion in the tissues to form sodium bicarbonate. This process, however, is slow and implies a cooperation on the part of the kidneys which will always be doubtful in severe affections.

It must therefore be maintained that a saline therapy is much inferior to the bicarbonate therapy as a means of combating acidosis, but may be a valuable and logical supplement to the bicarbonate therapy in such cases of acidosis in which the chloride values of the plasma have been reduced.

E. Alkalosis.

An increase in the bicarbonate value of the plasma above the normal will cause *alkalosis*. This condition being of considerable interest in connection with the treatment of acidosis, we shall here discuss alkalosis in somewhat more detail. In the last chapter it was mentioned that alkalosis chiefly occurs as a result of overdosing with sodium bicarbonate, more especially in circumstances in which the excretion of bicarbonate in the urine is defective owing to renal disease. In such diseases, too, in which, after treatment with alkali, bicarbonate is being formed in the organism as a result of the combustion of organic acids (especially keto-acids and lactic acid), there will be a possibility of a great increase in the bicarbonate content of the plasma. Such a condition will especially be present in a simultaneous alkali and insulin treatment of diabetic coma.

Besides being a result of overdosing with sodium bicarbonate, alkalosis may also occur in patients who lose large amounts of acid stomach contents by vomiting, thus especially in patients suffering from pylorospasm and pylorostenosis. As a consequence of the loss of chloride in the vomitings the bicarbonate content of the plasma will increase, the bicarbonate in the plasma being substituted for the chloride ions brought up (see Fig. 1).

With this complication, too, the clinical symptoms are uncharacteristic. Usually the patient complains first of fatigue and indisposition; and not rarely there is pronounced nausea. Not until the bicarbonate concentration has mounted to more

than 40 millimols does the characteristic symptom of *tetany* appear (in affections of the stomach called gastric tetany). With a further rise consciousness is affected and alkalotic coma sets in. It has not yet been established at what bicarbonate values death usually supervenes. The author has seen a rise in the bicarbonate value to 60 millimols without fatal outcome.

The treatment of alkalosis depends on its degree. If there is only an analytically demonstrable alkalosis without clinical symptoms no special therapy is called for. Previously the chief treatment of severe alkalosis consisted in intravenous injection of large amounts of saline. The chloride ions administered will replace the bicarbonate ions excreted in the urine, which will cause the bicarbonate content of the plasma to fall to the normal again. The therapeutic effect of the administration of saline is often striking: the convulsions cease, and there is a considerable improvement in the condition of the patient.

In more severe cases of alkalosis (with bicarbonate values exceeding 40 millimols) Cullen[32] and co-workers have lately, at the Children's Hospital at Cincinnati, successfully employed intravenous injection of dilute hydrochloric acid solution, a therapy which seems rational in the gravest degrees of alkalosis, and especially would seem to be indicated in cases in which the alkalosis is due to overdosing of bicarbonate in the presence of renal insufficiency. The necessary amount of hydrochloric acid is calculated by the following formula, converted from that of Cullen: C. c. of concentrated hydrochloric acid (36 p. c.) = (millimol plasma bicarbonate — 30) 0.063 · weight in kg.

The concentrated hydrochloric acid is diluted with 0.9 p. c. sodium chloride solution, at most 5 c.c. of concentrated hydrochloric acid being added to 100 c. c. of saline. The injection is made slowly and is suspended if symptoms of a distressing dyspnea set in.

III

Acidosis under Physiological Conditions

Lactic Acid Acidosis during Hard Physical Work.

In daily life acidosis occurs so frequently that it will be familiar to everybody, for during hard bodily work a considerable lactic acid acidosis will set in. The acidosis occurs especially during brief spells of hard work in which the production of lactic acid during the muscular work is so great that it cannot be removed as fast as it is formed. The lactic acid in the muscles is produced from glycogen, which during the contraction of the muscles is split up into lactic acid. In conditions in which the supply of oxygen to the muscular tissue is sufficient, $^4/_5$ of the lactic acid produced will be reconverted into glycogen at the end of the contraction, while the remaining $^1/_5$ undergoes combustion to carbon dioxide and water. If, on the other hand, the oxygen supply is insufficient in proportion to the amount of work, the resynthesis and the combustion of the lactic acid will not take place to its normal extent, and so the lactic acid will accumulate in the muscles and thence pass into the blood. While during rest the concentration of lactic acid in the plasma is only about 1–2 millimols (10–20 mg p. c.), the amount may rise during work to 10–12 millimols (i. e. to more than 100 mg p. c.). Such an increase will cause a corresponding reduction of the bicarbonate content of the plasma, which will be reduced from the normal c. 25 millimols to 12–14 millimols or almost half (see Fig. 4). The rapid development of the acidosis with removal of large amounts of carbon dioxide by the lungs will generally result in a violent dyspnea. After the work has ceased the acidosis will gradually subside, the lactic acid being converted into carbon dioxide and water, and transformed into glycogen.

An accumulation of lactic acid in the muscles corresponding to a plasma content of 10 millimols will practically render

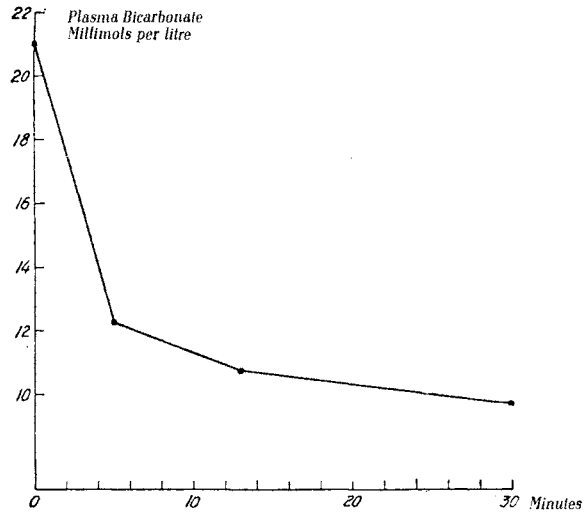

Fig. 4. Lactic acid acidosis in hard physical work. During the working experiment (1620 kilogrammeters per minute) the bicarbonate content of plasma is reduced to half its normal value. Constructed after Bøje ,0., »Der CO_2-gehalt des arteriellen Blutes während Muskelarbeit beim Menschen«. Skandinav. Arch. f. Physiol., *71:* 61, 1934.

further work impossible and will thus become a limiting factor in the output of work. This circumstance will also be of importance in athletics and sports in setting a limit to the possible reduction of the times of world records in certain sports events. In some cases it seems possible to improve the record by administration of bicarbonate, whereas conversely, the maximal output of work will be reduced with a pre-existing considerable acidosis (e. g. acidosis due to medication).[35, 36]

The acidosis of hard muscular work is, as already mentioned, due to the fact that the supply of oxygen is insufficient in proportion to the muscular work. A disproportion between the supply of oxygen and the lactic acid combustion will, however, also occur under conditions in which the oxygen intake and the transfer of oxygen to the tissue is defective, that is to say, in cardiac decompensation and circulatory insufficiency. This anoxemic lactic acid acidosis has thus the same course of development as the physiological; but as a result of its pathogenesis it must be termed pathological and will be discussed in a special chapter.

IV

Acidosis under Pathological Conditions

A. Acidosis due to Uncomplicated Loss of Alkali.

1. Fistula of the Small Intestine. 2. Biliary Fistula. 3. Bile Drainage. 4. Pancreatic Fistula.

In large and prolonged losses of intestinal secretion, bile, or pancreatic juice, a reduction of the bicarbonate content of the organism will regularly set in, these secretions being alkaline. It is understandable therefore that with fistulas of the small intestine, pancreatic fistulas, and following bile drainage, as also in the presence of biliary fistulas a considerable acidosis will often develop. Only if the intestinal fistula is located in the upper part of the duodenum, and the secretion removed consists chiefly of the stomach contents, will conditions be otherwise, since the loss of an acid secretion will, conversely, result in the development of an alkalosis, in the same way as when acid stomach contents are brought up.

In mild and moderate degrees, acidosis due to loss of alkali is the type most easily surveyed if the pathological picture is not complicated by infection or a severe peritoneal condition. After large losses of alkaline secretions, however, a grave dehydration will often set in, with symptoms of shock.

Even if the affections that may be referred to this group are not particularly frequent, there will nevertheless in most large surgical departments occur one or several instances of this form of acidosis in the course of a year. It is very important therefore to possess a knowledge of the complicating

acidosis as a cause of the more or less grave symptoms that set in. The treatment of this form of acidosis is especially satisfactory, since the condition is generally promptly improved after administration of isotonic sodium bicarbonate solution. The final prognosis for the acidosis, however, depends on the possibility of removing the cause of the loss of alkali by surgical operation.

Case record No. 1. Fistula of the small intestine.

(Own observation[89, 90], Ugesk. f. Læger, 97: 1212, 1935).

A housewife, aged 58, was admitted to Bispebjerg Hospital in Copenhagen in 1935 suffering from sarcoma of the small intestine. Laparotomy was performed with resection of the sarcoma. 4 days after the operation an intestinal fistula developed from which flowed abundant thin intestinal contents. 3 days after the appearance of the fistula the patient's condition, in spite of energetic saline treatment, was vere bad, with frequent vomiting, much reduced diuresis, and marked dyspnea. At this juncture a determination was made of the bicarbonate content of the plasma which showed the presence of acidosis with reduction of the bicarbonate concentration to 17.5 millimols.

Immediately after the analysis 1 litre of isotonic sodium bicarbonate solution was injected intravenously, whereupon a very considerable improvement in the condition was seen in the course of a couple of hours. The vomiting, nausea and dyspnea ceased. Shortly after the injection 100 c. c. of urine was excreted, which in spite of the administration of alkali showed an acid reaction. The treatment was repeated for the next two days, after which the acidosis was entirely relieved (27.0 millimols). At this time the condition was very satisfactory, and the patient took the ordinary full diet with a good appetite. Unfortunately 2 days after the last bicarbonate injection sudden collapse set in, during which the patient died with symptoms of acute cardiac decompensation.

Case record No. 2. Bile drainage.

(Own observation[89, 90], Ugesk. f. Læger, 97: 1212, 1935).

A tramway employee, aged 52, was admitted to the Bispebjerg Hospital in Copenhagen in 1935 for an affection of the bile duct. Cholecystectomy was performed and hepatic drainage instituted. One week after the operation symptoms of grave debility set in with dullness, fatigue, loss of appetite. The bile secretion was at this time about 1 litre in 24 hours. The plasma was examined and showed a reduction of the bicarbonate concentration to 17.2 millimols and a

rise in the value of the blood urea to 118 mg p. c. 1 litre of isotonic sodium bicarbonate solution was at once injected intravenously, *whereupon the symptoms subsided in the course of 20 minutes.* On the next day the blood urea had fallen to 80 mg p. c. and the alkali treatment was repeated. 4 days later the patient was again dull and apathetic, and the examination showed that a moderate acidosis had again developed (bicarbonate 15.3 millimols). 2 bicarbonate injections of 1 litre each were now given, after which the acidosis again subsided (bicarbonate 24.6 millimols) with complete relief of the symptoms. As the hepatic drainage was discontinued at this stage no further alkali treatment was given, and there was no later recurrence of the symptoms.

As far as the author knows, no observations are available in the literature of the bicarbonate content in the plasma in the presence of pancreatic fistulas in man. Gamble and McIver[52] however, in 1928 published convincing experiments on dogs provided with pancreatic fistulas. The result of one of these experiments is recorded here:

For the experiment was used a dog weighing c. 20 kg in which a fistula was made to the pancreatic duct, through which all the pancreatic secretion was emptied out. At the beginning of the experiment the bicarbonate content of the plasma was 26 millimols.

For the first 10 days after the operation the dog was lively and apparently felt well; as late as the 10th day the bicarbonate content of the plasma was only reduced to 19 millimols. After this, however, the dog grew increasingly dull and apathetic, and at last would hardly take either food or water. Analysis of the blood made on the 12th and 13th days after the production of the fistula showed the presence of a serious acidosis with reduction of the bicarbonate value to 12 millimols.

On the 14th day after the operation the condition was very grave, the extremities were cold, the pulse was accelerated, the blood pressure much reduced and there was violent acidotic dyspnea. Analysis of the blood showed a reduction of the bicarbonate content of the plasma to 7 millimols. On the afternoon of the 14th day 2 litres of 0.9 p. c. sodium chloride solution were administered intraperitoneally without any great effect, but the animal survived the following night. On the 15th day in the morning the condition was unchanged while the bicarbonate content of the plasma was still reduced to 7 millimols. 400 c. c. of 2 p. c. sodium bicarbonate solution were now administered in the femoral vein. In the afternoon the bicarbonate concentration had risen to 17 millimols while at the same time a considerable improvement was seen in the condition of the dog. The dog was later killed under anesthesia.

In this form of acidosis it is usually not difficult to carry through the bicarbonate treatment. After the acidosis has been relieved by bicarbonate dosing according to Van Slyke's nomogram, the further administration of alkali is planned, taking due account of the size of the continued loss of alkali. By repeated bicarbonate analyses it is possible to ascertain at any time whether there is a recurrence of the acidosis.

B. Acidosis due to Loss of Alkali Complicated with Infection and Intoxication.

1. Cholera. 2. Other severe diarrheas in adults (dysentery, meat poisoning, fungal poisoning). 3. Acute gastroenteritis in children.

In cholera and other severe diarrheas in adults and in acute gastroenteritis in children a considerable loss of alkaline secretion often occurs. This is especially the case if the upper sections of the intestines participate in the affection, as the intestinal secretion in these parts is more alkaline. Not rarely the diarrheas will bring about an enormous loss of total base, which, at any rate in cholera, often seems to be the chief cause of the development of acidosis (see p. 61, Table 3). The loss of alkaline secretion and total base is not, however, the only cause of acidosis. The infection and intoxication which are present also contribute to this; by injuring the cells of the tissues the intoxication produces a necrosis of these, with an abnormal production of organic and inorganic acids, and indirectly, through circulatory insufficiency and anoxemia, involves an accumulation of lactic acid as a result of defective oxygenation. It is possible, too, that certain bacterial products affect the intermediate cellular metabolism and reduce the oxidation of the tissues, which will likewise cause an increase in the lactic acid concentration in the tissues and in the blood (cf. also p. 122).

In those cases in which the disease is associated with the vomiting of acid stomach contents the development of acidosis is counteracted. In the simultaneous presence of diarrhea and vomiting, however, an extraordinarily rapid development of dehydration and shock is frequently seen, which in the most

severe cases of cholera and infantile diarrhea may have a fatal outcome in the course of a few hours. The dehydration, acidosis, intoxication and state of shock will frequently give rise to a severe uremia, already described in 1911 by Sellards[198] in cholera, later (1915) by Marriott in infantile diarrhea, and finally in 1917 by Lesieur[116] in choleriform diarrheas in adults (gastro-entérites urémigènes).

1. Cholera

»I have never yet seen one bad symptom attributable to it and I have no doubt that it will be found, when judiciously applied, to be one of the most powerful and one of the safest remedies, yet used in the second stage of cholera . . .«. Latta[112] in 1832 in the Lancet on the intravenous treatment with sodium chloride carbonate solution.

»The effects of this injection were almost magical« Miller[139] in 1832 in the London Medical Gazette, on the same treatment.

»The early administration of alkalies in cholera has been effective in preventing death from cholera«. Sellards and Shaklee[198] in 1911, on the intravenous treatment with isotonic sodium bicarbonate solution.

Despite the fact that it is almost 90 years since the cholera devastated Denmark as a regular epidemic, this disease still deserves special mention as the representative of a group of diseases in which acidosis occurs with special severity and frequency. The considerable similarity in the course of cholera, the severest forms of infantile diarrhea, and the more rarely occurring choleriform diarrheas in adults renders it probable that the observations and experience from the treatment of cholera may be referred with advantage to the cholera-like diseases occurring in our latitudes. In spite of the fact that cholera occurs in countries and under circumstances in which it is difficult to carry through scientific investigations, there is now available from the last 100 years so considerable a number of valuable observations concerning the acidosis and its treatment that numerous questions must now be said to have been cleared up.

Of outstanding importance for the understanding of the pathogenesis of acidosis in cholera are O'Shaughnessy's[154] investigations during the epidemic in England in 1831–32.

In a brief report to the Lancet »Experiments on the Blood in Cholera«, dated December 29, 1831, he gives an admirably clear account of his results, which he later finds occasion to elaborate in a longer paper[155] »Chemical Pathology of Cholera«. By analysing serum from cholera patients, O'Shaughnessy showed that the water content, the total salt content, and the amount of alkali*) were appreciably reduced, and at the same time he pointed out that the lacking salts, and particularly sodium carbonate, were present in great amounts in the patients' diarrheas. The article in question is so modern in its form and conclusions that it is difficult, when reading it, to keep the fact in mind that it was written more than 100 years ago (see Fig. 5).

It was not to be O'Shaughnessy himself, however, who was to draw the correct therapeutic conclusions from these observations**). The credit for being the first to employ intravenous injection of solutions of sodium chloride and sodium bicarbonate, the salts naturally present in the blood, to replace the salt, alkali, and fluid lost in the cholera diarrheas belongs to a general practitioner in Leith, Dr. Thomas Latta[112]. The first reports on the sensational results of this treatment are found in two letters by Dr. Latta's colleague,

*) The first demonstration of acidosis in cholera is presumably due to John David in India who had many years earlier (the date cannot be ascertained) found a considerable reduction of the carbon dioxide content in the respiration air of cholera patients (see W. Stevens, Observations on the healthy and diseased properties of the blood. London 1832. p. 486).

**) This is probably due to the fact that O'Shaughnessy shortly before on a more speculative basis had proposed another therapy for cholera, viz. the injection of the highly oxidised salts potassium nitrate and potassium chlorate (»Proposal of a New Method of treating the Blue Epidemic by the Injection of highly oxygenated Salts into the Venous System.« Lancet *1*, 366, 1831-32). O'Shaughnessy had hardly any opportunity of trying this treatment, which is only a matter for satisfaction, since it might have brought discredit on the intravenous sodium chloride bicarbonate therapy. Latta was beyond doubt the first to introduce the intravenous treatment in cholera (Lancet *2*, 1831-32, and *2*, 286, 1831-32) but he emphasises that it is the plasma analyses of O'Shaughnessy that have given him the idea of this treatment (Lancet *2*, 275, 1831-32). Incidentally, O'Shaughnessy himself later adopted Latta's treatment (editorial, Lancet *2*, 929, 1831-32). Conversely, Latta tried to »improve« his solution by introducing nitric oxide into the water before dissolving the salts (Lancet *1*, 173, 1832-33), possibly under the influence of the above-mentioned paper by O'Shaughnessy.

EXPERIMENTS ON THE BLOOD IN CHOLERA.

To the Editor of THE LANCET.

SIR,—Having been enabled to complete the experimental inquiries on which I have some time back been engaged in Newcastle upon-Tyne, I beg you will have the kindness to give insertion to the annexed outlines of the results I have obtained:—

1. The blood drawn in the worst cases of the cholera, is unchanged in its anatomical or globular structure.

2. It has *lost a large proportion of its water*, 1000 parts of cholera serum having but the average of 860 *parts of water*.

3. *It has lost also a great proportion of its* NEUTRAL *saline ingredients.*

4. *Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.**

5. Urea exists in the cases where suppression of urine has been a marked symptom.

6. *All the salts deficient in the blood, especially the carbonate of soda, are present in large quantities in the peculiar white dejected matters.**

There are other results of minor consequence, to which I will not at present allude, neither shall I *on this occasion* offer any observation on the practical inference to which my experiments may lead. In a few days a detailed report shall be published, in which the mode of analysis, &c. will be minutely described. It will be found, I regret to say, in every essential particular, to contradict that recently given by Hermann. All my experiments, however, have been publicly performed, and can be authenticated by numerous witnesses, a precaution I thought it necessary to adopt, lest it might be supposed that I impugned, without sufficient foundation, the accuracy of the Moscow professor.

May I add, that until the publication of my report, I shall deem the suspension of discussion on the results now introduced as a matter of personal courtesy and obligation. I am, Sir,

Your obedient servant,

W. B. O'SHAUGHNESSY, M.D.

London, 29 December, 1831.

Fig. 5. Reproduction of O'Shaughnessy's letter to The Lancet. December 29, 1831.

Dr. Robert Lewins[117], to the Board of Health in London, in which the effect is described as »most wonderful and satisfactory«. From numerous articles in The Lancet in the months that follow it appears that the treatment attained a considerable popularity and undoubtedly in several cases resulted in the curing of otherwise hopeless cases of cholera, since apparently it was not rarely possible to resuscitate

already moribund patients. The treatment met with much opposition but also early gained support in influential quarters. In an editorial article of June 2, 1832, The Lancet thus bestowed the highest possible praise on the new therapy, and particularly emphasised its scientific foundation, O'Shaughnessy's investigations, on which the treatment is based. To this very day it is a pleasure to read the well balanced and exhaustive considerations and views advanced in the periodical.

A perusal of the publications of 1832 conveys the impression that the therapy was principally applied in very severe cases of cholera, a fact which must be kept in mind in the evaluation of the results gained. In the above-mentioned article in The Lancet 5 recoveries out of 15 apparently hopeless cases are mentioned. Latta himself seems to have saved 8 out of 16, Girdwood[53] 5 out of 7 patients. The particulars concerning the saline solution employed are often somewhat uncertain, as it does not appear plainly whether sodium carbonate or sodium bicarbonate has been used. The sodium chloride concentration was usually 0.40–0.55 p.c., the concentration of sodium bicarbonate (or of sodium carbonate (waterfree?) in terms of the alkaline value of the bicarbonate) 0.1–0.25 p.c. In spite of the low alkali content the total amount of alkali administered was sometimes rather considerable on account of the great amounts of fluid used (often 10–15 litres); thus in two of Latta's cases it was c. 25 g of sodium bicarbonate, and in Weatherhill's[227] case c. 33 g. The beneficial effect of the treatment, however, was no doubt just as largely due to the effect on the state of shock, and on the dehydration, of the large amounts of water and sodium chloride administered.

It was soon realised by Doctor Latta and his colleagues that the immediate favourable effect of the treatment did not imply that the patient was out of danger. The condition required almost constant watching, and the injections had to be repeated at the first sign of a relapse. Thus Latta says after mentioning the primary astonishing improvement, »such symptoms, so gratifying both to the sick and the physician, must never allow the latter to relax in his care, — the utmost vigilance is still necessary. At first the change is so great that he may fancy all is accomplished, and leave the patient for a while. The diarrhoea recurring, he may find his patient after the lapse of two to three hours as low as ever.«

Medical science must be grateful to these physicians who, as will appear from their letters, worked day and night, constantly watching their mortally sick cholera patients, for affording the time to give a detailed report of their observations. Their contribution marks one of the most important therapeutic advances in medicine.

Case record No. 3. Cholera.

(»Malignant cholera«. Documents communicated by the Central Board of Health, London. Lancet, 2: 276, 1831-32).

The first patient who was treated by Doctor Latta with intravenous injection of an alkaline salt solution was an old woman on whom the usual remedies (probably calomel, opium, enemas etc.) had been tried without success, so Latta decided to try the intravenous treatment. He himself says about it: »She had apparently reached the last moments of her earthly existence and now nothing could injure her, — indeed, so entirely was she reduced that I feared I should be unable to get my apparatus ready ere she expired. Having inserted a tube into the basilic vein, cautiously — anxiously I watched the effects; ounce after ounce was injected but no visible change was produced. Still persevering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eyes, and fallen jaw pale and cold, bearing the manifest impress of death's signal, began to glow with returning animation; the pulse which had long ceased, returned to the wrist, at first small and quick, by degrees it became more and more distinct, fuller, slower and firmer, and in the short space of half an hour, when 6 pints had been injected, she expressed in a firm voice that she was free from all uneasiness, actually became jocular and fancied all she needed was a little sleep; her extremities were warm, and every feature bore the aspect of comfort and health.«

Doctor Latta now, from his experience of other, spontaneous recoveries of cholera cases, considered the patient out of danger and left her to attend to other patients. Shortly after, however, the diarrheas and vomiting recurred, she gradually sank and died 5½ hours later.

Thus this case became of importance not only by showing the primary effect of the injections, but at the same time it emphasised the necessity of a constant watching of the patients with a view to a repetition of the treatment in case of relapse.

The case records that follow emphasise the importance of intensive and repeated treatment.

Case record No. 4. Cholera.

(Same publication as the preceding case, Lancet, 2: 276, 1831–32).

A woman, aged 50, very destitute, who had not previously suffered from any grave disease was seized on May 13, 1832 at 4 a. m. with symptoms of severe cholera. When she was attended by Doctor Latta at about half past ten her condition already seemed hopeless. The pulse was quite gone even in the axillae and the condition so reduced that Latta only with some hesitation decided to try treatment with an alkaline salt water injection. In the presence of four other physicians he quickly injected 120 ounces (c.3.6 litres) of saline solution. The effect of this was like magic. The patient's consciousness returned, the cadaverous appearance of the body disappeared. Shortly after, however, diarrheas recurred, and 3 hours later the condition was again low. Again 120 ounces (c.3.6 litres) were injected with the same good result. She did not yet seem to be out of danger, however, so another 90 ounces of saline solution (c.2.7 litres) were administered, so that in the course of the first 10 hours a total of 10 litres of fluid was given. The recovery now proceeded rapidly; already 2 days later the patient could enjoy her first pipe of tobacco. She was now transferred to the cholera hospital so as to receive better care and was later discharged from there as well.

The following case record, communicated by Dr. Weatherhill, besides giving a convincing impression of the importance of the intravenous treatment of cholera also affords a striking example of the energy and solicitude of English practitioners 110 years ago.

Case record No. 5. Cholera.

(Weatherhill, T.:[227] *»Case of malignant cholera, in which four hundred and eighty ounces of fluid were injected into the veins with success.« Lancet, 2: 688, 1831–32).*

A blacksmith, aged 29, was seized with symptoms of cholera during his work on August 18, 1832. He was at once put to bed in his home and already a few hours later he felt better. After 3 days he felt quite well and — without the permission of his physician — got up and came downstairs to dine with his family.

At five o'cl. of the same afternoon he was, however, taken ill again, and this time the disease set in with such violence in spite of energetic treatment that already the next day at 7 o'cl. he was moribund. As Dr. Weatherhill now regarded the condition as

hopeless he decided to use the therapy indicated by Latta and immediately injected half a gallon (2 litres) of sodium chloride-sodium carbonate solution intravenously. The favourable effect appeared almost at once. First breathing grew more easy, then the circulation improved, and the skin became warm. This improvement which, in Dr. Weatherhill's words, was »truly delightful«, only lasted for half an hour, however, when he began to sink again. Another 2 litres of solution were therefore injected with the same good effect; the patient was again restored to consciousness and felt well (»he was himself again«). At 10 o'cl. a. m., 2 hours after the last injection the condition had again become grave. The patient perspired profusely, the extremities were cold, and there were symptoms of incipient collapse. Therefore 2 litres of alkaline saline solution were injected intravenously for the third time; this again resulted in considerable improvement, but the patient now began to pass large amounts of yellowish offensive fluid per anum. He quickly became exhausted from these diarrheas, chilly and almost pulseless. Therefore 2 more litres of solution were injected intravenously (4th injection) after which the patient soon regained his strength and under the impression of his improvement became quite cheerful. Even though the condition was now fairly satisfactory, it was still necessary to give injections again at 2 o'cl. and 5 o'cl. p.m. (3 and 2 litres) and at 9 o'cl. in the evening (2 litres).

Thus in the course of 14 hours, 7 injections comprising in all 15 litres of fluid had been given. After this the pulse remained full and regular, c.100, and the general condition so good that further treatment with injections was considered unnecessary. Apart from pronounced fatigue the recovery now proceeded rapidly.

Dr. Weatherhill concludes his report with these words: »It will readily be perceived that much time and attention were given to this case. Had there been less, it must have terminated in another way. In return, I possess the proud feeling of having been the means of rescuing a human being from death.«

With the termination of the cholera epidemic the interest in the intravenous injection of saline solutions waned, and this therapy was almost forgotten when 20 years later the disease again invaded England[210]. Nor was the injection of saline solutions used in Denmark during the great cholera epidemic in 1853, when 4,700 people were swept away in Copenhagen alone. At any rate, this treatment is not mentioned in Professor Fenger's[47] article »Observations on the Treatment of Asiatic Cholera« in Bibliothek for Læger nor in the other Danish medical literature of the period.

The efficacy of the treatment was rediscovered in 1884 by Cantani[23] of Naples, who speaks enthusiastically about the effect of subcutaneous alkaline saline injections in cholera cases. In a lengthy article in the »Berliner klinische Wochenschrift« for 1886, he describes his experience of this therapy which, without any knowledge of O'Shaughnessy's and Latta's publications, he founds on an independent demonstration of reduced alkalinity of the blood in cholera and on the observation of the highly acid reaction of the urine of cholera patients. The saline solution used by Cantani contained 0.4 p.c. of sodium chloride and 0.3 p.c. of sodium carbonate (corresponding to c. 0.5 p.c. of sodium bicarbonate). Not only was the immediate effect of the treatment spectacular, but the final results, too, were very satisfactory, as 114 out of 187 patients recovered, corresponding to a percentage of 69.

It is interesting to note the almost identical words used by the various physicians in their description of the astonishing primary effect of the treatment. Thus Cantani describes the effect in the following phrases which are highly reminiscent of Latta's and Lewins' accounts: »Die kalten, cyanotischen, vertrockneten, stimmlosen Kranken, die pulslos und wie leblos dalagen, belebten sich nach der heissen, subcutanen Salzwasserinfusion oft wunderbar in wenigen Minuten, bekamen Puls und Stimme wieder und sassen sogar vonselbst im Bett auf — und mehrere genasen hierauf dauernd —.«

Only a few years later, in 1892, Germany and France were again visited by a cholera epidemic which, especially in Hamburg, spread very rapidly and widely. The epidemic left traces in a voluminous literature which treats very thoroughly the results of the parenteral therapy. It is beyond doubt that numerous dramatic recoveries were attained (thus we hear of »zauberhafte Wirkung«), but most of the recoveries were unfortunately shortlived so that the death-rate was hardly much affected. From the various reports it appears that a 0.7 p.c. sodium chloride solution without any addition of alkali was generally used for injection, the total amount of fluid injected being 1–1.5 litres. With our present knowledge it seems probable that the modest results can be explained by the omission of bicarbonate, and a too cautious use of fluid.

The most recent period of research on choleraic acidosis begins in 1910 with investigations by the American Sellards[195] during an epidemic in Manilla on the Philippines. Sellards

then made the interesting observation that while the urine of normal subjects was rendered alkaline after ingestion of about 5 g of sodium bicarbonate by mouth, cholera patients required intravenous injection of 30–90 g of sodium bicarbonate before the urine became alkaline. Further Sellards showed that the urea content of the blood was usually much increased in cholera, that in other words uremia was frequently present, and finally he made the clinical observation that the uremia was often accompanied by marked dyspnea.

In a later article by Sellards and Shaklee[198] (1911) we find the first analyses of the blood of cholera patients performed with a modern technique (evacuation of the blood after the addition of acid, and measurement of the amount of carbon dioxide extracted). These analyses show the presence of a considerable acidosis. Thus in a patient on the fourth day of illness the bicarbonate content was found to be reduced to 11 millimols, and in another patient on the third day of illness to 7 millimols. In the latter patient there was marked dyspnea. Unfortunately more detailed clinical information is lacking, but Sellards' data are quite sufficient to establish the frequent occurrence of acidosis and uremia in cholera and the not infrequent occurrence of acidotic dyspnea.

Of great importance also are Sellards' and Shaklee's observations on the effect of the intravenous bicarbonate therapy in cholera, as these investigations which were made on a large number of patients, convincingly show the advantage of bicarbonate solution over sodium chloride solution in the treatment of acidotic uremia. The investigations comprise 155 cholera patients, 78 of whom were treated with intravenous injection of Ringer's solution, 77 with sodium bicarbonate solution (0.5–1.5 p.c.). Out of the 78 patients treated with Ringer's solution 12 died of uremia, while among the 77 treated with sodium bicarbonate there only occurred one death from this cause; the total number of deaths in the two groups was 49 and 32 respectively.

The favourable effect of the intravenous injection of bicarbonate appears with especial distinctness from the ability of this therapy to induce diuresis in the presence of anuria. In briefer spells of anuria diuresis usually set in a few hours after the injection of bicarbonate (see Fig. 6). The occurrence of diuresis was often followed by a rapid rise in the urea concentration of the urine; thus in the case shown in Fig. 6 the

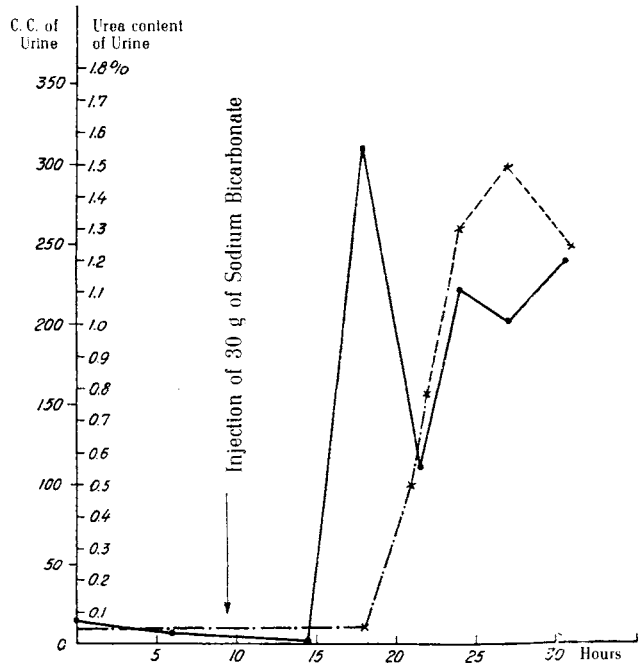

Fig. 6. Effect on diuresis of intravenous injection of sodium bicarbonate in cholera.

In spite of the existing anuria considerable diuresis set in 4 hours after injection of 30 g of sodium bicarbonate. At the same time the urea concentration of the urine rose from 0.05 p. c. to 1,50 p. c. The case terminated with the recovery of the patient.

After Sellards, A. W. and Shaklee, A. O., Philippine J. Sc., *6:* 52, 1911,

diuresis
urea

concentration rose from 0.05 to 1.3 p.c. in the course of 5 hours. Even after anuria of 24 hours' duration it was often possible to induce diuresis by a bicarbonate injection, while this could rarely be accomplished after the injection of Ringer's solution. In a single case, in which a total of 90 g of sodium bicarbonate was injected, diuresis was re-established after 3 days' anuria. The first portion of urine, which was passed 18 hours after the injection, was colourless like water; the subsequent portions contained increasing amounts of urine pigment, and the case terminated with the recovery of the patient.

Sellards concludes his observations on the diuresis-inducing effect of bicarbonate solutions in cholera with the follow-

ing words: »The effect of bicarbonate is therefore very striking, since at practically any period during the stage of reaction or even of uremia massive injections will cause a secretion of urine. Moreover a polyuria often develops promptly in contrast to the scanty secretions in the cases treated with normal saline.« As will appear from the sequel, Sellards' and Shaklee's observations on the favourable effect of a bicarbonate therapy in uremic cholera cases have been fully confirmed by later investigators and have caused the lives of thousands of people to be saved.

Sellards' work has been carried on by Rogers in India who, since 1905, had thoroughly studied the use of saline solutions in the presence of cholera. At the time when Sellards' publication appeared Rogers had already succeeded in reducing the death rate from cholera from 60 to 30 p.c. by the use of a slightly hypertonic saline solution and oral ingestion of potassium permanganate. An essential feature of Rogers' treatment was the administration of very large amounts of fluid and frequent repetition of the treatment if necessitated by the condition of the patient, that is to say, on the whole a treatment along the lines indicated by Latta and his colleagues. In 1915 Rogers introduced Sellards' bicarbonate therapy as a supplementary treatment *with the result*[177, 179] *that the mortality from acidotic uremia fell from 11.1 to 3.2 p.c.* (see Table 2). Of decisive importance for the attainment of favourable results was, according to Rogers, the early institution[178, 180] of alkali treatment, since bicarbonate injections in the latest stages of uremia often caused symptomatic improvement only. Already in his first publication of 1915 Rogers therefore recommends repeated determinations of the plasma alkali so as to avoid undue delay of the bicarbonate treatment. He used a 2 p. c. sodium bicarbonate solution which, as in Sellards' material, had an exceedingly favourable influence on the anuria; in one case it was even possible to re-establish diuresis after 6 days' anuria.

From Rogers and his co-workers,[180, 181] too, we have valuable investigations on the bicarbonate content of the plasma in cholera; though made with a somewhat less reliable technique than Sellards' determinations they clearly show the frequent occurrence of acidosis and its bearing on the prognosis.

The value of Rogers' observations must be viewed against

Table 2.

Total cholera mortality and deaths from uremia before and after the use of alkalies.

After Rogers, L., Lancet, *193:* 745, 1917.

Without alkalies

Years	Cases of cholera	Uremia deaths	Percentage
1912	170	24	14.1
1913	200	17	8.5
1914	222	25	11.2
1912—14	592	66	11.1

With alkalies

Years	Total Cases	Uremia deaths	Percentage
1915	226	6	2.6
1916	204	8	3.9
1917	154	5	3.2
1915—17	584	19	3.2

the background that they were made in a country where cholera is endemic and where there are, therefore, opportunities of examining a great number of patients. Thus an article[180] in The Lancet from 1921 is based on 2000 cases. Compared with this two European works on the treatment of cholera from the beginning of the great war by Rosenthal[185] and Elias,[41] must be termed modest, but they merit attention because the authors had no knowledge of Sellards' and Rogers' investigations, but, on the basis of their own observations on the clinical picture of the disease, instituted intravenous treatment with bicarbonate solution. The investigations both of Rosenthal and Elias were carried out in the field under particularly difficult circumstances.

Rosenthal,[185] who served at the cholera hospital in Philipoppel in Bulgaria during the Servian-Bulgarian war, noticed that numerous patients presented a clinical picture that was highly reminiscent of diabetic coma, as there was typical Kussmaul respiration and unconsciousness. He therefore tried parenteral administration of 3–5 p. c. sodium bicarbonate solution on 24 moribund patients with the astonishing result that half of these, in his opinion hopelessly sick, people recovered. Following the injections respiration became normal, the somnolence disappeared, and the patients ate and drank of their own accord. Several of them even got up.

Elias'[141] work is from the campaign in Russian Poland and Volynia in the years 1914–15. He too mentions the »startling similarity between the clinical picture of cholera and the dyspneic form of diabetic coma.« The alkali treatment of these patients was intravenous, a 4 p. c. sodium carbonate solution being administered, and the therapy was especially tried on patients on whom repeated saline injections had been ineffective. During the injection of the concentrated alkaline solution consciousness gradually returned, by degrees the respiration grew calmer, and the patients began to talk. Almost regularly an improvement of 12–14 hours' duration set in, which in many apparently hopeless cases was the beginning of the patients' recovery. Often, however, it was necessary after the lapse of 24 hours to give one more sodium carbonate injection. According to the estimate of Elias the treatment was life-saving in one-fourth of the cases.

From more recent years we have a publication by Tomb[212] (1926), who like Sellards prefers isotonic sodium bicarbonate solution to hypertonic solutions. Tomb entirely agrees with Sellards and Rogers about the value of the bicarbonate treatment as a means of preventing acidotic uremia and warmly recommends the use of this therapy as a routine method.

Finally, of the latest investigations on cholera we may mention those of Liu, Fan and Wang,[120, 121] (1933) and Loh and Tai[123] (1936). The work of Liu and his co-workers was carried out at Peking during an epidemic in the summer of 1932, and comprises studies on 28 cholera patients. In all the patients, acidosis was observed upon admission; the average plasma bicarbonate value was 14.1 millimols, the lowest value 8.2 millimols. Liu, Fan and Wang's determinations of the total base value and the concentration of the individual acid constituents in the plasma in 13 untreated cholera cases deserve special mention, *for these analyses are the first that afford a complete insight into the pathogenesis of the choleraic acidosis.* The figures show a very considerable total base reduction as well as an increase in the lactic acid and phosphate values (see Table 3).

Loh and Tai's investigations were carried out at the Chinese Infectious Diseases Hospital at Shanghai and in agreement with Liu, Fan and Wang's work show an average reduction of the plasma bicarbonate value to 11.1 millimols in cholera patients in the first stage of the disease. In patients who

Table 3.

Salt content of the plasma in cholera.

After Liu, S., Fan, C., and Wang, S. »Acidosis in Cholera« Proc. Soc. Exp. Biol. & Med. *30:* 419, 1933.

	Acute stage millimols	Convalescence millimols
Total base	138.4	152.5
Bicarbonate	14.8	30.7
Chloride	92.2	99.2
Phosphate	4.0	1.8
Protein	15.8	13.5
Lactic acid	6.8	2.3
Undetermined acids	4.8	5.0
Total acid	138.4	152.5

The values represent the average of the analyses in 13 cases of cholera. The table shows that in the acute stage there occurs a total base loss of 14.1 millimols as the chief cause of acidosis.

were very low, a considerable rise in the residual nitrogen in the blood was further very frequently found. Loh and Tai's report is, incidentally, of special interest owing to its publication of blood analyses during the course of the disease. Since these analyses appear to be the first that are recorded in the literature, they are given below. The figures show a rapid rise in the bicarbonate content of the plasma during the recovery. It should be noted that in one of the cases recorded, over 40 litres of alkaline saline solution were injected.

Even though a high death rate must necessarily be expected in so grave a disease as cholera it will appear from the works mentioned in this chapter that by an early administration of large amounts of saline solution it is possible to effect a great reduction in the mortality. Since acidosis and uremia occupy a prominent place in the clinical picture special importance attaches to the intravenous bicarbonate therapy in the treatment of the disease. And as a matter of fact, the results reported show that this therapy will bring about a rapid and often spectacular clinical improvement and may to a great extent prevent the development of the dreaded acidotic uremia. Consequently, as already pointed out by Rogers in

Table 4.

The bicarbonate content of the plasma during recovery from cholera.

After Loh, V. and Tai, T., »A Study of the Blood in Cholera«. Chinese M. J. *50:* 651, 1936.

Duration		Plasma bicarbonate millimols	Residual nitrogen mg p.c.	Alkaline saline injected, litres	Secretion of phenolsulphonphthalein 1st hour p.c.	2nd hour p.c.
			First case			
Days	Hours					
	5	11.8	52	—	Anuria	
	8	12.3	42	6	Anuria	
7	6	11.2	175	—	5	5
12	12	22.4	60	—	20	18
23	12	27.2	36	—	50	10
			Second case			
3	12	5.9	130	13	—	—
4	12	10.2	101	8	18	3
10	16	30.2	120	—	20	20
19	16	31.7	30	21	45	15

1915, it must be considered particularly necessary to make frequent determinations of the bicarbonate content of the plasma during the course of the disease, in order to be constantly informed as to the degree of acidosis, and so have a possibility of combating it.

2. Other Severe Diarrheas in Adults.

(Dysentery, meat poisoning, fungal poisoning.)

In a number of severe diarrheas in adults a clinical picture may sometimes be seen which is highly reminiscent of cholera and of the gravest cases of acute gastroenteritis in children. Such cases of diarrhea with symptoms of excessive dehydration are, however, on the whole not very frequent. Thus in the Central Epidemic Hospital at Lyon Lesieur[116] only observed

this choleriform type in 33 out of 1230 patients with acute diarrhea. The similarity of the picture to cholera has caused the adoption of the clinical terms »Cholera nostras« and »entérites cholériformes«. Epidemiologically the affections are generally dysenteric or may be referred to the group gastroenteritis acuta Salmonellosa (»meat poisoning«); fungal poisonings, too, and acute arsenical poisoning may give a similar picture.

Whereas fairly thorough bacteriological analyses are at hand concerning these forms of disease, biochemical studies are very scanty. The observations so far published, however, warrant the conclusion that in choleriform diarrheas, just as in cholera, there may occur considerable acidosis and uremia. In the cases described by Lesieur the blood urea had thus risen to 150–600 mg p.c. (»gastroentérites urémigènes«). Apart from some few case records only a single work on the occurrence of acidosis in this group of diseases is available. It is a series of investigations made by Bondarenko and Bogdanovich[17] (1935), from the university clinic at Minsk, comprising determinations of the bicarbonate of the plasma in 37 cases of bacillary dysentery in adults. In patients who were very low an average reduction of the bicarbonate content to 16 millimols was found during the first days of sickness; the lowest value observed was 11.6 millimols. The severest degrees of acidosis occurred in the cases in which the intoxication was most pronounced. In patients with milder attacks the reduction was more moderate. After recovery a considerable rise in the values was usually noticed, similar to that shown by Loh and Tai during recovery from cholera.

Of the published cases we quote the following three. The first carefully investigated case was reported by Heimbech[71] in Kristiania in 1928.

Case record No. 6. Acute gastroenteritis.

(Heimbech, J.,[71] »Acidose ved akut enterit« (Acidosis in acute enteritis). Norsk Mag. f. lægevidensk., 89: 131, 1928.)

A carpenter, aged 62, was suddenly taken ill on July 6, 1927 with vomiting and diarrhea. The symptoms persisted the following days and caused great thirst. There was no abdominal pain or fever, but as there was no improvement, the patient was admitted to the Ullevaal Hospital in Kristiania on July 9.

The physical examination on admission showed nothing out of the ordinary except tenderness in the umbilical region. The temperature was 36°, the pulse 96, small and regular. There was no dyspnea.

The following day the condition was appreciably aggravated. The patient had not passed water since admission and there were symptoms of severe dehydration; the skin could be lifted up in folds which remained. The hands were cyanotic and cold, the tongue was half-dry and coated. The abdomen was still soft, there was distinct splashing on palpation. At this stage the blood was analysed and revealed the presence of a considerable acidosis and uremia, the bicarbonate concentration of the plasma being reduced to 9.5 millimols and the blood urea increased to 227 mg p.c.. In the course of the day 1 litre of saline solution was injected subcutaneously. The patient was further given tea and barley water to drink, which he could keep down.

On July 11 the patient passed the first portion of urine which contained traces of albumen and some few granular casts. The diarrhea, however, persisted both on this and the two succeeding days. On the 12th of July the analysis of the blood was repeated, and revealed a further aggravation of the acidosis and uremia (plasma bicarbonate 8.2 millimols, blood urea 256 mg p.c.). Only now was it realised that acidosis was present, and the treatment was adjusted in accordance herewith. In the period 13-16 July, 30 g of sodium bicarbonate were administered daily by mouth. Already on the 14th of July the bicarbonate value of the plasma had risen to 17.4 millimols and on the 16th of July to 36.5 millimols (after the administration of presumably 120 g of sodium bicarbonate in all, which according to Van Slyke's nomogram corresponds to an overdose of about 50 g), so that a moderate alkalosis had developed. At the same time the blood urea concentration had fallen to 79 mg p.c.. The alkalosis caused no discomfort and the patient was discharged well on August 5.

Case record No. 7. Acute gastroenteritis.

(Merklen, P. and Gounelle,[136] *»Gastro-entérite aiguë cholériforme avec azotèmie e.t.c.« Progrès méd., 1: 713, 1934).*

A waiter aged 38 fell ill at the beginning of April 1932 with pain in the abdomen, vomiting and persistent, non-offensive diarrheas. Gradually increasing debility finally necessitated hospitalisation.

On his admission to the medical department in Strassbourg on April 27 the patient was very feeble and emaciated and could only speak in a weak voice. The skin was dry and could be lifted up in folds which remained. The temperature was normal, the blood pressure 65/30. There was tenderness upon palpation of the abdomen, corresponding to the descending colon. The analysis of the blood

showed a moderate acidosis (plasma bicarbonate 13.5 millimols), considerable increase in the blood urea concentration (192 mg p.c.) and much reduced plasma chloride values (80 millimols).

In the days that followed the vomiting and diarrhea persisted and the condition grew gradually worse in spite of treatment with glucose and saline injections. The patient became more and more cachectic and death supervened on May 19 after incrasing debility. On May 6 the bicarbonate concentration was 14.4 millimols, on May 18 it was 16 millimols. The blood urea steadily increased and shortly before death was 288 mg p.c.. Treatment with sodium bicarbonate was not given during the course of the disease.

Case record No. 8. Acute mushroom poisoning.

(Aubertin, C. and Patey G.,[7] *»Intoxication fongique (Syndrome phalloidien de type algido-choléri forme) avec anurie et azotèmie.« Bull. et mém. Soc. méd de hôp. de Paris,* 51: *233, 1935).*

A man, aged 41, was admitted to the La Pitié Hospital in Paris on October 16, 1934 with choleriform symptoms. 2 days before admission he had eaten some mushrooms of doubtful origin on a journey. The next day violent diarrhea with almost continuous evacuation of the bowels occurred, accompanied by greenish vomiting and abdominal pain. After some hours, cramps of the lower extremities and of the hands also set in.

On admission the patient was extremely reduced but quite conscious. The skin was pale-gray and flabby, the eyes sunken and the cheeks hollow. The tongue was dry, the extremities chilly, the pulse almost impalpable. There was mild dyspnea but only a moderate increase of temperature (38.2°).

Shortly after admission 500 c.c. of glucose saline were injected subcutaneously without any great effect. The next day (October 17) the condition was nearly unchanged. The patient had had a bad night and had not yet passed water. In the course of the day he passed 25 c.c. of urine which showed a strong albumen reaction. Analysis of the blood revealed the presence of uremia with increase of the residual nitrogen to 160 mg p.c.. As on the previous day 500 c.c. of physiological saline solution were administered subcutaneously as well as 30 c.c. of 20 p.c. sodium chloride solution intravenously.

On October 18 the patient felt better, the vomiting being less frequent. At this stage the bicarbonate content of the plasma was determined and showed the presence of a moderate acidosis (16.4 millimols). The chloride value was 95 millimols, while the residual nitrogen concentration was still appreciably augmented (175 mg p.c.). On this day, too, the diuresis was sparse, 30 c.c., but next day, when

the improvement in general health was beyond doubt, 1500 c.c. of urine were excreted at the same time as the residual nitrogen value fell to 95 mg p.c.. In the days that followed recovery proceeded rapidly just as the diuresis remained normal. On October 22 the bicarbonate concentration was 22.6 millimols and the plasma chloride and residual nitrogen values were likewise normal.

The patient was discharged well on October 27.

3. Acute Gastroenteritis in Children.

In Denmark acute infantile gastroenteritis is the commonest cause of acidosis as a result of loss of alkali. Even though the accompanying intoxication is often the dominant factor in the clinical picture and the course of the disease, and frequently constitutes the actual cause of death, acidosis is nevertheless so common and grave a complication that the recognition of its presence and its treatment with isotonic sodium bicarbonate solution becomes an important task in modern pediatry.

Acute gastroenteritis is one the chief causes of infant mortality. Thus in the period 1925-30 about 500 children died annually of the disease in Denmark. In France[144] the corresponding figure was 16,000, in Spain 47,000, and in England 5,500. With the increasing improvement in sanitary conditions the mortality from infantile diarrhea has decreased considerably in most countries. This decrease has also been observed in Denmark where acute gastroenteritis has only claimed about 300–350 deaths annually since 1935.[134] Even these figures are, however, so serious that all possible means should be employed to rescue more of the children from death. This would seem to be of special significance in gastroenteritis in which recovery, if it occurs, is as a rule complete.

We have already mentioned that death from infantile diarrhea may occur in the absence of acidosis, and in a previous chapter (see p. 18) it was pointed out that even severe acidosis in children need not entail appreciable clinical symptoms. This, however, must not delude us into believing that acidosis in children is a complication of no consequence. It has been shown conclusively that acidosis may be the true cause of death in gastroenteritis. The significance of the

acidosis is further seen plainly from that relief in respiration which often occurs following treatment with alkali, a fact known to American pediatricians already 25 years ago. Quite frequently acidosis is probably the straw that breaks the camel's back. Since, however, the disease is often predominantly characterised by the intoxication, the treatment must not in all cases (as in uncomplicated alkali deficiency) be expected to be effective.

It is to be deplored that precisely in this grave disease, in which the severe forms have a death rate of about 50 p.c. (see Fig. 8), the knowledge of the diagnosis and treatment of the acidosis should be so limited. A consistent employment of the bicarbonate therapy would surely not fail to influence the mortality statistics.

The causes of acidosis in acute infantile gastroenteritis are mentioned on p. 47. As in cholera they are to be found partly in the loss of alkali in the diarrheas (Holt,[75, 76, 78] Meyer[137]) partly in an abnormal accumulation of organic acids (Clausen,[25] Hartmann,[76, 69] Csapó[29, 31]), either as a result of the intoxication itself, or because of an anoxemia caused by the latter, which again conditions a deficient oxidation of lactic acid. The keto-acids, on the other hand, seem to be of little significance for the causation of the acidosis (Marriott and Howland,[79, 80] Friderichsen[49]). The reason why acute gastroenteritis as a rule gives rise to a much severer acidosis in children than in adults is probably that the watery evacuations of children are considerably greater in relation to their body weight than those of adults, so that the disease in this respect can be almost compared to cholera in adults, where acidosis, as previously stated, is a very frequent finding. In some cases, especially in the so-called secondary gastroenteritis, which occurs following upon acute parenteral infections (e.g. suppurative otitis media) in infants, the disease is frequently not accompanied by severe diarrheas. In these cases it seems more to be the metabolic and circulatory disturbances produced by the intoxication than the loss of alkali in the stools which is of significance for the development of the acidosis.

The first realisation of the presence of acidosis in gastroenteric affections in children dates from the close of the last century. Thus in 1897 Czerny[93] called attention to the striking similarity in the respiratory type of animals poisoned by acid

and of moribund infants with severe gastroenteric affections. He further showed that in acute gastro-enteritis there was an increased excretion of ammonia in the urine.

The first blood analyses with a view to acidosis in gastro-enteritis come from Pfaundler[167] in 1905 but the electrometric measurement of the hydrogen-ion concentration was still at that time somewhat uncertain. A few years later, in 1912, Salge[187] was able to demonstrate a considerable increase in the hydrogen-ion concentration (i.e. a severe acidosis) in a moribund and intoxicated child suffering from gastro-enteritis.

From 1915 a series of valuable and significant observations on the problem of acidosis in acute gastroenteritis begin to appear in America, especially from Howland, Marriott and their co-workers. Thus Howland and Marriott[79, 80] demonstrated that children with severe diarrhea suffered from an acidosis, the clinical symptom of which was dyspnea, while laboratory investigations showed it to be characterised by a reduction of the carbon dioxide content of the alveolar air, a (colorimetrically determined) increase of the hydrogen-ion concentration, and an increased tolerance towards sodium bicarbonate. These results were later confirmed by the adoption of Van Slyke's gasometric method, when it was found by Schloss and Stetson[192] that the bicarbonate content in the plasma of children suffering from severe diarrhea was often considerably reduced (5–21 millimols). Further, Howland and Marriott were the first to show that acidosis in acute gastro-enteritis is not due to the presence of keto-acids in the blood; they also demonstrated that the acidosis was frequently attended by considerable uremia.

From the years that followed there are several works at hand concerning the organic acids as a cause of acidosis in infantile diarrhea. Thus Clausen[25] already in 1925 found the lactic acid content much increased in several cases of infantile diarrhea, a finding confirmed a few years later (1928) by Hartmann[67, 69] in a somewhat more extensive series of investigations. Csapó and his co-workers,[29, 31] too, (1934–1936) pointed out the very frequent occurrence of organic acidosis in this disease. Of special significance for the understanding of the acidosis problem in acute gastroenteritis was further Friderichsen's[49] thesis for the doctorate, »On Acidosis in Infants« for in this work investigations were for the first time made on the hydrogen ion concentration in the plasma of a

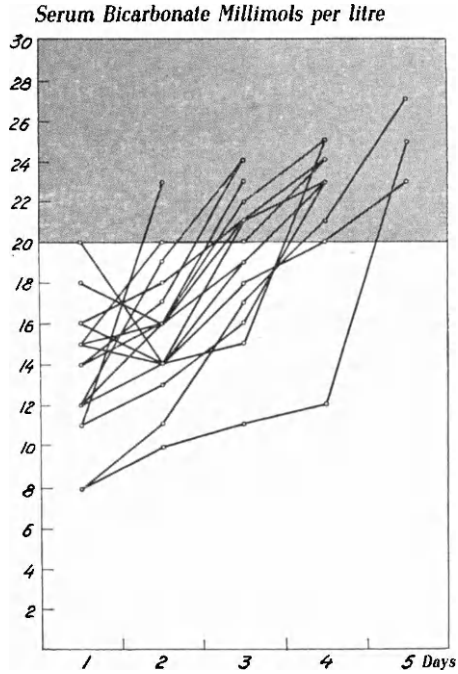

Fig. 7. The bicarbonate content of serum in acute gastroenteritis of children during the spontaneous recovery of the disease.
The shaded section of the figure denotes the area of normal values.
From Kirk, E., Ugesk. f. Læger, *101:* 1291, 1939.

large number of patients during the spontaneous course of the disease. It is to be regretted that this fine publication, which is not available in translation, is hardly known outside the boundaries of Denmark. Friderichsen's investigations, which comprise 17 cases of gastroenteritis, showed, in accordance with the experience of American pediatricians, that in severe cases of infantile diarrhea a considerable acidosis will often occur, and that this acidosis is not due to accumulation of keto-acids. The investigations further revealed that in the cases terminating with recovery, the acidosis is very quickly relieved spontaneously, the values often becoming normal in the course of 2–3 days. A corresponding rapid rise in the bicarbonate values of the serum during recovery was demonstrated by means of a more modern technique by the present writer[97] in 1938 during the investigation of a large number of cases of acute infantile gastroenteritis not treated with bicarbonate (see Fig. 7).

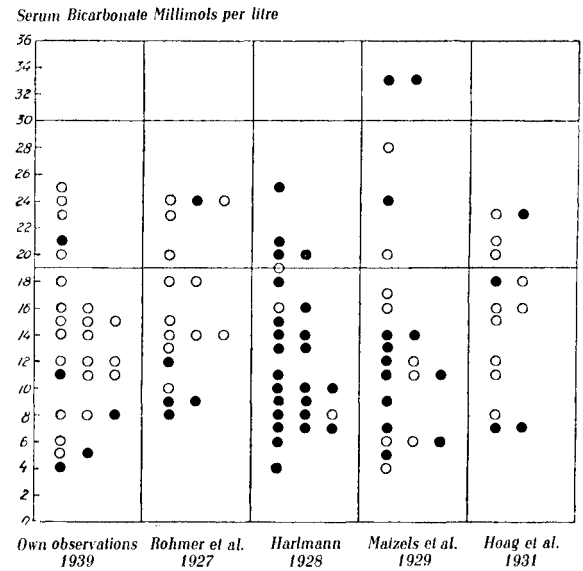

Fig. 8. The bicarbonate content of serum in acute gastroenteritis of children.
The horizontal lines delimit the area of normal values.
Open circles: recovered.
Filled in circles: dead.
From Kirk, E., Ugesk. f. Læger, *101:* 1291, 1939.

While Friderichsen's material showed a certain correlation between the severity of the disease and the degree of acidosis, such a correlation is not plainly apparent on a comparison of the observed bicarbonate values in the plasma and the course of the disease in 106 cases of acute gastroenteritis reported by various other authors. As will appear from Fig. 8 which exhibits the results of these investigations, a fatal outcome of the disease was observed in numerous cases with a normal or but slightly reduced bicarbonate content in the serum, while conversely, a reduction to 4 millimols of the bicarbonate value in one instance did not result in death (see also Case records Nos. 11 and 13).

Considering the often prominent part played by the bacterial intoxication in the signs and symptoms of the disease, a more regular correspondence betwee the degree of acidosis and the severity of the clinical symptoms was hardly to be expected.

The variable character of the disease is probably the reason why the frequency of the acidosis is very differently reported

in the publications at hand. Thus Frauenberger[48] found a reduction of the bicarbonate content of the plasma to below 14 millimols only in 46 out of 276 cases (17 p.c.), while Hamilton, Kajdi and Meeker[61] demonstrated an appreciable reduction in 12 out of 15 instances. Among the cases shown in Fig. 8 the frequency of acidosis is also high.

The difference in the clinical symptoms of acidosis in adults and in children is mentioned in Chapter I, where it was pointed out that children are far less sensitive than adults to a reduction in the bicarbonate content of the blood. This was first shown experimentally in 1928 by Drucker[38] who by the administration of ammonium chloride and calcium chloride was able to produce severe acidosis in healthy children without apparent effect on them. It has been confirmed by the present writer[97] in the above-mentioned series of investigations on children with acute gastroenteritis. In the absence of intoxication it was not unusual to see the children sitting up in bed playing, though they had bicarbonate values (6–8 millimols) which in adults would generally cause incipient or well developed coma. With a further reduction of the bicarbonate content of the plasma, however, a severe dyspnea may often be seen. As already stated, the correlation between the acidosis and the air hunger is plainly apparent in such cases from the relief of the dyspnea that will often follow bicarbonate treatment (see e.g. Case record No. 12).

In very severe degrees (3–5 millimols) the acidosis may undoubtedly give rise to disturbances of consciousness and coma, but consciousness may also be seriously affected in severe cases of gastroenteritis not accompanied by acidosis, probably as a result of the effect of the bacterial toxins on the central nervous system.

The intravenous or subcutaneous administration of sodium bicarbonate solution in the treatment of severe infantile diarrhea gained ground in American pediatry about 1916, after Howland's and Marriott's fundamental researches on the acidosis problem. At this juncture, however, it was not clearly understood that it was of importance to treat the dehydration in addition to the acidosis, and instead of isotonic sodium bicarbonate solutions, hypertonic solutions of 4–5 p.c. were generally used, so that only up to 35 p.c. of the

amount of water corresponding to the salt was administered. Even though the momentary result of the treatment was favourable, since the dyspnea decreased and the general condition was improved, the final results were with a few exceptions bad, the outcome being often unsatisfactory. Only after Marriott, Schloss, and other pediatricians had pointed out the importance of making up the loss of fluid by using more dilute sodium bicarbonate solutions did it prove possible to save the lives of the children in a greater number of cases.

The methods of parenteral treatment of gastroenteritis have varied a good deal during the last 20 years, so that it is not possible to present a large group of cases of infantile diarrhea consistently treated with alkali. In Europe the psysiological saline therapy seems to have been predominant, at any rate in Denmark, while alkali has only rarely been added to the solution for the direct combating of the acidosis. In America, too, the use of non-alkaline or only slightly alkaline saline solutions has become widespread, especially in the form of solutions of salt mixtures (Ringer's fluid, Tyrode fluid, Locke's fluid, »plasma salt solution« etc.) with and without the addition of glucose. However valuable these solutions may be for the treatment of salt deficiency and dehydration, they are, as explained on p. 39, of less value in combating the acidosis present. The use of these solutions in authoritative quarters has no doubt contributed to throw the original bicarbonate therapy into the shade.

Of great importance for the combating of acidosis in gastroenteritis was the introduction by Hartmann[69, 70] in 1930 of a racemic sodium lactate solution, in 1/6 molar concentration for parenteral administration. The unquestionable value of sodium lactate solution in the treatment of acidosis meant an essential advance over the use of neutral saline solutions in the treatment of gastroenteritis. On the authority of Hartmann the lactate treatment has gained considerable popularity in America. Some confusion has arisen, however, by Hartmann's later introduction of a new solution, »Hartmann's Combined Solution«, which contains the salts naturally present in the plasma and in addition sodium lactate, but the latter substance in such small amounts that the lactate concentration is insufficient for the treatment of a more serious acidosis.

It was stated on p. 37 that in the author's opinion it is less rational to use a sodium lactate solution*) than an isotonic sodium bicarbonate solution, since the effect of the lactate solution is slower and more uncertain, as it is essential for obtaining an alkali effect that the lactic acid should undergo combustion to form carbon dioxide and water, that is to say, bicarbonate. Since, however, the lactic acid concentration in the blood in acute gastroenteritis, as already mentioned, is frequently spontaneously increased owing to circulatory insufficiency with anoxemia, the administration of lactate in this affection seems less rational. It is of considerable interest that in America, too, objections have been raised against the use of the lactate solution for combating acidosis in infantile diarrhea. Thus Minot, Dodd, and Saunders[143] have shown that the combustion of lactate is often much reduced in the presence of guanidine (see p. 121), a compound which has not infrequently been observed in greatly increased concentration in the blood in acute gastroenteritis with intoxication[37, 142]. Of still greater significance are the clinical investigations carried out by Cullen[32] at The Children's Hospital in Cincinnati. From his therapeutical results in acute gastroenteritis it appears that, while the use of 1/6 molar sodium lactate solution has proved satisfactory in milder degrees of acidosis, this therapy often fails in severe cases of acidosis, whereas the treatment with sodium bicarbonate solution was found to be of great value, both in the milder and the more severe forms (»in acute acidosis we find that it is much safer to use sodium bicarbonate«).

Considering the experience gained from the treatment of cholera mentioned in the introduction, it must also be warmly recommended in spite of the as yet rather scanty clinical material, to institute treatment with an isotonic bicarbonate solution in severe cases of acute infantile gastroenteritis. The easiest way of administering the isotonic solution is to use flasks with Seitz filtered 1.3 p.c. sodium bicarbonate solution (see p. 31). The contents are heated by immersing the flask in warm water before the injection, which is done sub-

*) The use of a lactate solution in the treatment of acidosis may seem downright peculiar considering the fact that in gastroenteritis an increase in lactic acid is often present as the cause of the acidosis. With the injection of sodium lactate solution, however, *sodium* is also introduced, which, by the combustion of the lactate, renders possible the formation of sodium bicarbonate.

cutaneously with a syringe in doses of 100–300 c.c. The treatment is repeated every 3 or 4 hours, while the bicarbonate content of the serum is checked (the bicarbonate determination is made on blood from the heel or ear according to the micro-method described on p. 196). In case of chloride deficiency a physiological sodium chloride solution is further administered. In inanition of more than 24 hours' duration the administration of 5 p.c. glucose solution will also be indicated; and this treatment may likewise be desirable even if the ketonemia is insignificant, in order to reduce the protein destruction of the tissue cells.

The first case record shows a fatal outcome of a case of severe infantile gastroenteritis, despite the fact that the acidosis was relieved by bicarbonate therapy.

Case record No. 9. Acute gastroenteritis.

(Own observation).

A girl 4 months old was admitted to the Children's Hospital at Fuglebakken in Copenhagen on October 4, 1938. She had been ill for 5 days with bloody vomiting, and numerous thin slimy stools. When admitted she was terribly low, unconscious, cyanotic, and dyspneic with dilation of the nostrils on inhalation. The temperature was 39.8°. From the time of admission till the next morning (October 5) at 9 o'cl. a total of 450 c.c. of saline was administered subcutaneously, apparently without effect. In the morning there was still marked cyanosis and dyspnea (respiration 88, moaning), and the child was still unconscious and had high fever (40°). A blood sample was now taken from the heel and it was noticed that the vasomotor reaction was poor, as the puncture could only with difficulty be made to bleed. The analysis showed the presence of a severe acidosis, the bicarbonate content of the serum being 4 millimols or only 1/6 of the normal (the record illustrates the insufficient effect of the saline therapy on the acidosis). After the blood sample had been taken, 100 c.c. of 1.3 p.c. sodium bicarbonate solution were injected subcutaneously.

At 1 p.m. the condition was nearly unchanged. The child, however, seemed less limp and moved a little. The injected bicarbonate solution had been entirely absorbed. There had been no further vomiting or diarrhea, but the child had not yet passed water. The temperature was 41.5°, the respiration 86. The bicarbonate determination was repeated and showed a rise in the bicarbonate value of the serum to 8.7 millimols. When the heel was punctured

for the blood sample it was noticed that the blood flowed more freely than before. After the analysis a further 150 c.c. of isotonic sodium bicarbonate solution was injected subcutaneously.

At 5 p.m. the child was slightly less cyanotic, the respiration was 84, somewhat less moaning, there was still dilatation of the nostrils on inhalation. She had not yet voided but by percussion the bladder was found to be distinctly distended. The blood analysis showed a rise in the bicarbonate content of the serum to 15.0 millimols.

In the hours that followed the child vomited a little now and then and passed a couple of watery offensive stools. No appreciable change occured in the condition and the child died at 7 p. m. without regaining consciousness.

In this case the acidosis can hardly be supposed to have been the actual cause of death, for the bicarbonate content of the serum was normal or only slightly below normal when death supervened. It must be assumed, therefore, that death was caused by the effect of the bacterial toxins on the central nervous organs and the circulatory system.

The next case record shows a favourable course of a moderately severe case of acute gastroenteritis treated with bicarbonate.

Case record No. 10. Acute gastroenteritis.

(Own observation).

A boy, 5 months old, was admitted to The Children's Hospital at Fuglebakken in Copenhagen on May 30, 1938 at 2 p.m.. 3 weeks before admission he had had an influenza-like illness with an affection of the ears and the last few days before the gastroenteritis set in, had had a cold in the head. On the morning of May 29 he was taken ill, passing numerous offensive stools, and in the course of the day had diarrhea 16 times in all. On the day of admission there were 8 stools in the forenoon. Before the admission the physician who sent him to hospital had instituted treatment with castor oil.

When admitted the child was somewhat low, languid and limp, but fully conscious. The temperature was 38.8°, there was no cyanosis but distinct dyspnea with a respiratory rate of 52. The child was at once given sterile water to drink and later in the afternoon 80 c.c. of saline subcutaneously. At 8 p.m. determination of the bicarbonate content of the serum was made, revealing the presence of severe acidosis (6.4 millimols).

In the course of the night and the next morning repeated injections of saline were given subcutaneously (300 c.c. in all). The condition in the morning was slightly worse, but improved somewhat

in the course of the forenoon. At 2 p.m. the respiration was 56, the pulse 184. At this stage a blood sample was taken for bicarbonate determination. It showed a concentration of 11.2 millimols, so that a quite considerable rise in the bicarbonate value had occurred simultaneously. Since the condition of the child still caused anxiety, 150 c.c. of isotonic sodium bicarbonate solution were injected subcutaneously at 2.15 p.m..

In the hours that followed a rapid improvement was seen in the patient's condition. Already at 5 p.m. the respiration frequency had fallen to 40 and the pulse to 164, at 9 p.m. to 36 and 128. In the evening the child looked perfectly well with normal turgidity and only slightly increased temperature (38.1°). A bicarbonate analysis showed that the acidosis had been relieved, the bicarbonate concentration being now 19.8 millimols.

The next case record reports an extremely grave case of acute gastroenteritis, in which bicarbonate therapy was instituted immediately after admission. In the course of 9 hours it was possible to raise the bicarbonate content of the serum from 5.4 millimols to a normal value of 21 millimols. Simultaneously a spectacular improvement of the condition was seen.

Case record No. 11. Acute gastroenteritis.

(Own observation).

A boy, 3 months old, was admitted to The Children's Hospital at Fuglebakken, Copenhagen, on October 24, 1938, at 5 p.m.. He had been taken ill on October 22 with numerous thin, green, slimy stools, and on October 23 had further had several bloody vomits.

When admitted the child was very low, unconscious, with pallid, cyanotic colour and with considerable reduction of turgidity. He seemed to be highly intoxicated and limp. The temperature was 38.7°, the respiration 84, and there was distinct dilatation of the nostrils on inhalation.

Immediately after admission, at 5 p.m., the bicarbonate was determined on heel blood and revealed the presence of a severe acidosis (bicarbonate of the serum 5.4 millimols). Owing to the poor vasomotor response it was only with difficulty that sufficient blood drops were obtained for the analysis. Immediately after this, 150 c.c. of isotonic sodium bicarbonate solution were injected subcutaneously.

Already at 9 p.m. the condition had improved appreciably. There was less cyanosis but the colour was still somewhat grey. The respirations had decreased from 84 to 64, and there was now no longer any dilatation of the nostrils on inhalation. Another sample of blood

was taken from the heel, and it was noted that the blood now flowed more freely. The analysis showed a rise in the bicarbonate value to 8.6 millimols. After this, 150 c.c. of isotonic bicarbonate solution were again administered subcutaneously.

About 3 hours later, at 11.45 p.m., the child's condition had improved still more, though there had been a single bloody vomiting. The cyanosis and the grey colour of the skin had disappeared. The turgidity was natural and *the child was entirely conscious,* though somewhat fretful. Although the temperature was 39.5°, the respiration was still only 64. Analysis of a blood sample showed that the bicarbonate value of the serum had by this time risen to 12.2 millimols. After obtaining this sample a third injection of 150 c.c. of bicarbonate solution was given and already after an hour it was fully absorbed.

4 hours later (October 25, at 4 o'cl. in the morning) the condition was still very satisfactory. Since the last injection the child had passed one offensive stool and had wetted himself abundantly. Owing to his constant querulousness it was not possible to count the respiration frequency accurately. Another bicarbonate determination showed that the acidosis was now relieved, (21.2 millimols), so the bicarbonate was discontinued. At 5 o'clock the same afternoon the temperature had fallen to 38.2° and the respiration to 52.

On the 26th of October the child had in every respect a natural appearance, and the bicarbonate value was normal (25.8 millimols).

The next case illustrates the effect of bicarbonate administration on acidotic dyspnea in infantile diarrhea. It was not until very large doses of bicarbonate had been given that it was possible to relieve the acidosis.

Case record No. 12. Acute gastroenteritis.

(Own observation).

A girl, aged 2, was admitted to the Medical Department of the Holstebro District Hospital on June 18, 1941.

She had been taken suddenly ill on June 10, passing numerous thin offensive stools with a slight admixture of blood, and now and then vomiting. The physician who was called in found the temperature increased to 39.4° and instituted a treatment with boiled water and castor oil. On the two following days there were still repeated diarrheas, but on June 13 the condition was much improved, the child now only passing a few semi-solid stools. At this stage the mother again began to give the child milk, after which the diarrheas recurred, accompanied by a pain in the abdomen. In the days that followed the patient grew steadily worse. On June 17 the physician noticed that the child was distinctly dyspneic, and it was decided to hospitalise her.

When admitted the child did not appear very ill. The temperature was normal, 37.6°, the pulse 116. There was some reduction of the turgidity of the skin and considerable dyspnea with accelerated, deep respiration (frequency 40). No cyanosis or dilatation of the nostrils on inhalation, nor any decrease of consciousness. An analysis of the blood showed the bicarbonate content of the serum to be much reduced, 6.2 millimols, which confirmed the assumption of the acidotic character of the dyspnea. 300 c.c. of isotonic sodium bicarbonate solution were at once injected subcutaneously as a first treatment.

On June 19 the condition was nearly unchanged. The child had only passed one thin stool and had one small ejection. There was still distinct dyspnea with a respiratory frequency of 46-40. As the analysis of the blood did not show any appreciable improvement in the acidosis (7.1 millimols), 500 c.c. of sodium bicarbonate solution were injected subcutaneously.

Next day the dyspnea had somewhat abated. The respirations were only 32 and less deep. There was still considerable acidosis (10.0 millimols) so another 500 c.c. of sodium bicarbonate solution was given.

On the 21st of June the respiration was 27, the diarrhea had ceased, and the child had a better appetite. The bicarbonate content of the serum was again determined and showed a continued but slow rise of the values (15 millimols). 500 c.c. of isotonic sodium bicarbonate solution were therefore again injected subcutaneously, with the result that the bicarbonate concentration in the serum was normal next day (22.0 millimols) and the respiration natural, 24. There was no recurrence of the gastrointestinal attacks and the child was discharged well on June 25.

The last case record shows the effect of a bicarbonate therapy in a case of gastroenteritis with severe acidosis in which two weeks' previous treatment had failed to improve the condition.

Case record No. 13. Acute gastroenteritis.

(Own observation).

A girl, aged 19 months, was admitted to the Medical Department of the Holstebro District Hospital on August 22, 1941. She had been well until 15 days before admission when symptoms of acute gastroenteritis set in. For the next two weeks the child had diarrhea 5-6 times daily and vomited rather frequently. The temperature was not increased, but the condition was steadily aggravated, the patient lost weight and became somewhat absent. Dietary treatment, including apple powder preparations, and medical enemas were ineffective.

When admitted the child was semiconscious with half-closed upturned eyes but otherwise did not seem very ill. There was no cyanosis or dyspnea and no demonstrable reduction of the turgidity of the skin. In spite of the normal temperature (36.8°) the heart rate was distinctly accelerated, 140.

The bicarbonate content of the serum was at once determined, and the presence of a severe acidosis was revealed (3.0 millimols). Immediately after the determination, at 3 p.m., 200 c.c. of isotonic sodium bicarbonate solution were administered subcutaneously and this treatment was repeated 3 hours later. Already at 8 p.m. the condition was appreciably improved. There had been a couple of watery stools but no vomiting; the child looked considerably better, was mentally alert, and willingly drank citric acid milk.

In the course of the night, three more injections were given of 200 c.c. of sodium bicarbonate solution (at 10 p.m., 5 a.m. and at 8 a.m.), the total amount of bicarbonate administered in the first 15 hours being thus 1 litre. After the last injection the bicarbonate content of the plasma was again determined, and the analysis showed that the acidosis had now entirely disappeared (23.4 millimols). The further recovery was uneventful. Already the next day (August 24) the stools were natural. The child was discharged quite well 6 days after admission.

C. Acidosis due to Persistent Anacid Vomiting.

1. Hyperemesis Gravidarum. 2. Anorexia Nervosa.

Acidosis in this group of affections has not so far been subjected to thorough investigation. It is the author's conviction, however, that this form of acidosis, too, has a claim to attention, since it seems to occur fairly often and occasionally to give rise to dangerous conditions (see e.g. Case record No. 16).

It has already repeatedly been mentioned that vomiting of acid stomach contents will cause a rise in the bicarbonate content of the plasma, that is to say, an alkalosis. If, on the other hand, the stomach contents are neutral, the vomiting will result in a diminution of the total base content of the plasma and a corresponding reduction in the bicarbonate value (see Fig. 1). If, moreover, under these circumstances alkaline duodenal contents flow back into the stomach, a direct loss of alkali will take place. If the vomiting persists a considerable increase in the keton content of the blood may

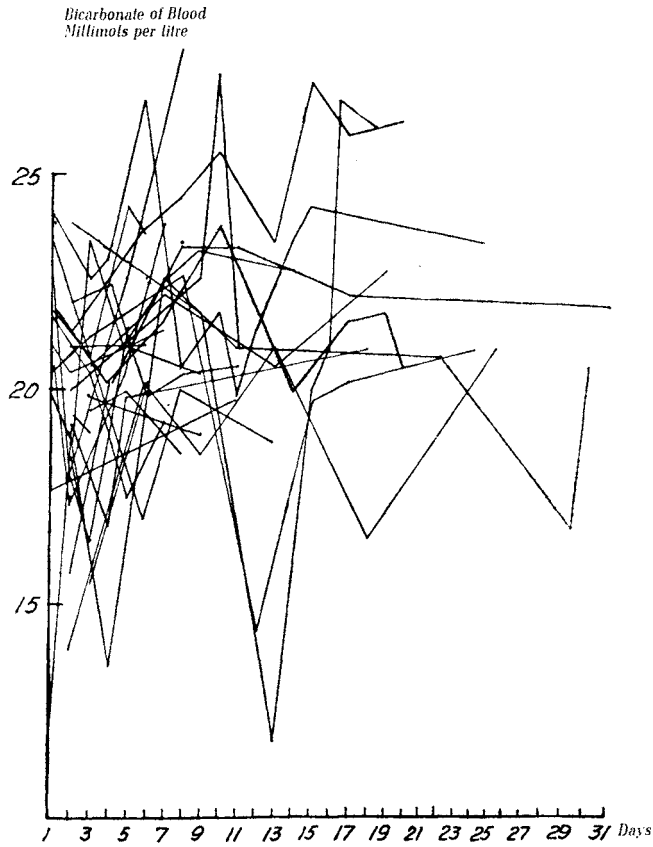

Fig. 9. The bicarbonate content of the plasma in hyperemesis gravidarum.
After Glassman, O., »A Study of Hyperemesis gravidarum with special Reference to Blood Chemistry«, Surg., Gynec., and Obst. *66:* 858, 1938.

occur, owing to the deficient intake of carbohydrate, that is to say, an inanition acidosis will develop, which will increase the bicarbonate reduction caused by the electrolyte deficiency (see p. 113).

This form of acidosis will especially be seen in affections in which the vomiting is considerable and persistent, thus in hyperemesis gravidarum in its more serious forms, and in nervous anorexia, in which affections gastric anacidity is a frequent finding. Since in these conditions, too, there will be a considerable loss of chloride, it is understandable that

the chloride content of the plasma will likewise often be much reduced.

Investigations on the bicarbonate content af the plasma in hyperemesis gravidarum have been reported by Peckham[160] (1939) and by Glassman[54] (1938) who both found very variable bicarbonate values (see Fig. 9). These findings entirely correspond to what might be anticipated, seeing that patients whose secretion of hydrochloric acid is intact will have a tendency to develop alkalosis, while the presence of gastric anacidity affords conditions for the development of acidosis. As a rule, however, no very considerable rise in the bicarbonate concentration will occur, since the inanition ketonemia will counteract the development of alkalosis. In the severest degrees of the disease, acidosis seems to be a frequent finding (Weil[42], Laudat[42]) and with values below 15 millimols, according to Herrick[149], indicates a serious prognosis.

For the treatment of the acidosis French clinicians have successfully employed injection of 4 p.c. sodium bicarbonate solution as well as administration of insulin and glucose. Both therapies seem well indicated (though the use of isotonic sodium bicarbonate solution instead of the concentrated solution is recommended). The administration of the bicarbonate relieves the acidosis and the total base deficiency, while the injection of glucose causes a reduction of the ketonemia.

The acidosis in nervous anorexia has not previously been recorded in the literature apart from a case reported by Barbaro-Forleo[12] (1938) and one reported by the author[92] (1939). The first bicarbonate-treated case of severe acidosis in this disease was observed by the author in 1941 and is quoted below (Case record No. 16).

The case record that follows shows the occurrence of severe acidosis in a young girl suffering from nervous anorexia.

Case record No. 14. Anorexia nervosa.

(Barbaro-Forleo[12] »Sulle chetosi non diabetiche degli adulti«. Archiv. di Patologia e Clin. med., 18: 37, 1938).

A girl, aged 17, was admitted to the Medical Department of the University Hospital of Pavia on October 12, 1936. She had been well and normally menstruated until 8 months prior to the admission when after a febrile angina there occurred constant vomiting with great debility. On the whole the condition was somewhat variable,

but gradually pronounced cachexia set in. Shortly after the vomiting had begun the menstruation grew irregular and for the last 5 months before admission there had been amenorrhea.

Upon admission the patient complained of pronounced fatigue, nausea and headache. There was copious vomiting and transitory clouding of consciousness. She was extremely emaciated with dry desquamating skin and sunken abdomen. The urine contained traces of albumen and gave a strong acetone reaction, just as the vomitings contained considerable amounts of acetone. An analysis of the blood showed that the bicarbonate content of the plasma had been reduced to 10 millimols.

A glucose and insulin therapy was instituted, after which the acetonuria decreased. The vomiting, however, persisted with varying intensity, so that it became necessary to adopt tube feeding. About a fortnight after admission a typical hysterical fit was observed. The patient was at last persuaded to eat spontaneously after which the weight slowly increased. On repeated analyses the basal metabolism was found to be distinctly reduced (65 p.c., 70 p.c.). After 3 months the first menstruation occurred. The patient was discharged well on October 17, 1937, about one year after admission.

Case record No. 15. Acidosis with anacid vomiting.

(Own observation,[92] *Ugesk. f. Læger,* 101: *328, 1939).*

A male physician, aged 38, who had been suffering for 13 years from cardiospasm, was admitted in 1938 to the Medical Department B of the Rigshospital of Copenhagen. In 1926 Plummer therapy had been twice employed with transitory good results. Following dilatation treatment with a bougie in 1929, peritoneal symptoms, however, set in. Laparotomy was performed, but no lesion of the peritoneum could be demonstrated. After the operation an appreciable aggravation of the condition occurred, the vomitings growing more frequent and abundant in the years that followed. They sometimes occurred for several days running and were then often accompanied by pronounced debility and slight clouding of consciousness.

One month prior to hospitalisation the patient had returned from his summer holiday. During the vacation he had been quite free from symptoms, but shortly after returning to work he again began to vomit 5 or 6 times daily. The vomitings were as a rule small, consisting chiefly of saliva, but sometimes larger and bile-coloured. 5 days before the admission there was a sudden aggravation of the condition, the patient vomiting incessantly, about 50 times in 24 hours. Between the vomitings he drank water and weak tea, whereas it was impossible for him to swallow solid food. When on the morning of the 4th day semiconsciousness developed the patient was taken to the hospital in an ambulance.

Upon admission he was extremely reduced, slightly absent, restless

and excited, asked repeatedly for water to drink and at intervals had projectile vomitings. These were bile-coloured and did not react to Congo paper or blue litmus paper. There was no cyanosis but distinct dyspnea, the respiration being both deep and accelerated, c. 36 per minute. The skin was warm with normal turgidity, there was increased arterial pulsation at the neck, but no thyroid enlargement. Stethoscopic examinations of the heart and blood pressure were normal. There were no signs of tetany and the physical examination showed nothing out of the ordinary.

An analysis of the blood made directly after admission revealed a moderate acidosis, the bicarbonate concentration of the serum being reduced to 15.2 millimols, whereas the serum chloride content was only moderately reduced (93 millimols), and the blood urea was normal (14 mg p.c.). The colour of the serum was slightly icteric (icterus index 12).

1 litre of physiological saline was at once injected subcutaneously and 1 mg of atropin sulphate and 1.5 c.c. of Sol. hypnopheni Pharm. Dan., after which the condition quickly improved and the vomiting ceased. In the course of a few hours the patient became quite lucid and was able to keep down liquid food. The dyspnea likewise decreased, whereas the increase in the respirations persisted throughout the first day. 10 hours after admission 450 c.c. of urine were passed; it contained urobilin, and traces of albumen, bile pigment and keton bodies. The urine further reacted strongly to Fehling's and Almen's tests, but showed no fermentation with ordinary yeast. In repeated analyses the blood sugar proved normal.

The next day the acidosis had disappeared (24.6 millimols) and the respiration was normal. There was no tendency to vomit. The patient ate an ordinary diet with a good appetite, though the fluoroscopic examination showed a considerable constriction of the esophagus and much delayed passage of the food through the cardia. A bromsulphalein test made 3 days after the admission showed 10 p.c. dye retention (30 minutes after injection). The metabolism which was distinctly increased (130 p.c.) the first days was normal in later tests. The patient was discharged well 9 days after admission.

The last record shows a case of acidosis in nervous anorexia which seriously influenced the general health. By means of an isotonic sodium bicarbonate therapy prompt relief of the condition was possible.

Case record No. 16. Anorexia nervosa.

(Own observation).

A sempstress, aged 40, was admitted on August 15, 1941 to the Medical Department of the Holstebro District Hospital in an extremely reduced condition.

It was learned that for 8 years she had been subject to dyspepsia

with epigastric discomfort, a poor appetite, and occasional vomiting. For many years she had followed a strict diet and had lost a good deal in weight. The patient had gradually become increasingly tired, brooding, and stolid, with pronounced anorexia, which was a constant source of anxiety to those around her. At last she did not do any proper work. 3 weeks before admission strong nausea occurred with numerous vomitings, up to 10-15 in 24 hours. Simultaneously she grew more and more drowsy and somewhat semiconscious.

When admitted the patient was extremely emaciated and distinctly semi-conscious. The turgidity was much reduced and the tongue quite dry. There was no dyspnea or cyanosis, and physical examination revealed nothing out of the ordinary, especially no symptoms of an acute abdominal disease.

Analysis of the blood immediately after admission showed the bicarbonate content of the serum to be reduced to 15.4 millimols, while the serum chloride value was only moderately reduced (89.6 millimols). There was considerable acetonemia, the total keton content of the blood determined by the method of Van Slyke and Fitz being 67 mg p.c., corresponding to an acid value of 14.3 millimols. There were no symptoms of uremia (blood urea concentration 20 mg p.c.).

2 litres of isotonic sodium bicarbonate solution were immediately injected intravenously whereupon the condition was appreciably improved, the patient becoming more alert and the tongue moist. On the next day (August 16) the condition was still satisfactory. In the course of the night the patient had voided and there had only been one small vomiting which did not contain free hydrochlorid acid. Analysis of the blood showed a rise of the bicarbonate value to 19.4 millimols.

Now another litre of isotonic sodium bicarbonate solution was injected intravenously followed in the course of the day by 3 litres of physiological sodium chloride solution containing 50 g of glucose, after which the acidosis was entirely relieved (22.1 millimols). In the next days there was still occasional vomiting; but the patient retained plenty of fluid and the diuresis was constantly over 1500 c.c. in 24 hours. Since there was still considerable unwillingness to take food supplementary nourishment was started on August 18 through a duodenal tube. During this treatment the condition continued to improve, and the nausea and vomiting ceased. X-ray examination of the stomach at this stage showed pronounced atonia with the pyloric part situated on a level with the 4th lumbar vertebra. After 4 weeks' stay at the hospital the appetite was satisfactory: every day the patient, in addition to her dinner, consumed 10 slices of bread and butter, 2 eggs, several glasses of cream and 1 bottle of Pilsner beer. She was discharged on September 11 without special complaints.

D. Acidosis Caused by an Abnormal Production of Acid.

1. Diabetes mellitus. 2. Ketonemic vomiting in children. 3. Inanition acidosis. 4. Acidosis in anoxemic conditions (Cardiac decompensation, peripheral circulatory insufficiency, shock, severe anemias). 5. Acidosis in anesthesia.

1. Diabetes Mellitus.

»The fact that one has to keep on arguing for the use of bicarbonate when it is needed is one of the things that makes one worry about the ability of the human mind to accept information. Because alkali is not needed in most cases of diabetic coma it makes it all the more necessary to determine the CO_2 content and use it when it is needed.«

Glenn Cullen (1939) in a letter to the author.

Among the clinical forms of acidosis, diabetic coma, on account of its frequency and gravity, is undoubtedly the most important, at any rate in adults. The recognition of acidosis as a complication in diabetes has been of the greatest significance for the treatment of the disease, and has in addition contributed much to a more thorough understanding of the carbohydrate and fat metabolism. Apart from O'Shaughnessy's observations on cholera, diabetic coma was the first clinical form of acidosis which was recognised (Stadelmann 1883). There is hardly any field in which medical treatment has celebrated greater triumphs than in the insulin treatment of diabetic acidosis, the lives of thousands of people having been saved since Banting and Best's discovery of insulin in 1922.

This discovery naturally divides the history of coma therapy into two periods, the first of which comprises the years 1883–1922, the second the time since 1922. The latter period is entirely characterised by the insulin therapy in its various forms and by the often outstanding results obtained by this treatment. The author, however, is anxious to emphasise that in spite of the consistent use of insulin treatment there are still many individuals who die from diabetic

coma. Thus Bertram[16] in a survey of 1007 coma patients treated with insulin found a death rate of 29 p.c., while Baker[9] had a mortality of 15.7 p.c. among 104 coma patients treated in the Mayo Clinic in the period 1923–34. It is probable that no small number of these deaths might have been avoided by a supplementary intravenous treatment with bicarbonate (Kirk[93] 1938). It is therefore greatly to be deplored that the interest in the alkali therapy has been almost entirely eclipsed after the introduction of the insulin treatment. In the author's opinion the alkali therapy has by no means become superfluous, but on the contrary has become even more important than before the introduction of insulin, since it is now possible by means of insulin to secure to the patients a desirable existence after the relief of the coma. In other words it is of greater importance now to rescue the life of a comatose diabetic than it was 25 years ago.

Diabetic acidosis is the result of an abnormal production of keto-acids: acetoacetic acid and β-hydroxybutyric acid, which are formed in excessive amounts upon the breaking down of the fats, in conditions in which the carbohydrate metabolism is defective. Both acetoacetic acid and β-hydroxybutyric acid are stronger acids than carbonic acid and by their accumulation in the blood*) will cause a reduction of the bicarbonate content of the plasma, the acids taking the place of the bicarbonate (see Fig. 1). The resulting reduction of the bicarbonate concentration will usually correspond to the molar concentration of the keto-acids. While normally there are only traces of keto-acids in the plasma (1–2 mg p.c., 0.1–0.3 millimols) the content in diabetic coma will not infrequently rise to 30 millimols. With such considerable increases, besides the amount of bicarbonate the chloride content of the plasma may also be diminished.

In addition to the accumulation of keto-acids there are other factors which contribute to the development of the acidosis. Thus the excretion of the keto-acids in the urine in combination with sodium and potassium will involve a loss of total base which will cause a reduction of the total base content of the serum. This reduction is often considerable; thus Peters and his co-workers[162], in an investigation of 26 cases of diabetic coma, found an average reduction of c.

*) The occurrence of acetonemia in diabetic coma was first pointed out by Petters[166] in a chemical investigation in 1857.

13 millimols. The reduction of the total base column (see Fig. 1) will involve a similar reduction of the total acid column which, as already mentioned, will affect the bicarbonate concentration and give rise to an aggravation of the acidosis. The total base deficiency in connection with the loss of fluid by the excretion of sugar and by vomiting will cause an often excessive dehydration with clinical symptoms which quite frequently reach the same degree as in cholera. The disturbances arising in the circulation are accompanied by anoxemia and oliguria with the possibility of an abnormal production of lactic acid and retention of inorganic acids (phosphates and sulphates). To this must finally be added the fact that in diabetic coma renal lesions[225] will often be present, which will further contribute to a retention of acids in the organism.

If we consider the various causes of the acidosis, it will be understandable that it is not only a ketonemic acidosis but may also be due to the presence of other organic acids (lactic acid[66, 135]) and inorganic acids, as well as to the development of a total base deficiency. The knowledge of this is important for the understanding of the effect of the intravenous bicarbonate treatment in cases in which the insulin therapy proves ineffective.

As in other forms of acidosis the organism will try to counteract the acidosis by excretion and neutralisation of the acids. To a certain extent the keto-acids may be excreted as free acids in the acid urine; the greater part, however, are neutralised before excretion by combination with sodium, potassium, or ammonia. As previously stated, a very considerable increase in the excretion of ammonia in the urine is often encountered in diabetic coma; in severe cases it may rise to 10 g in 24 hours. The excretion of the keto-acids as ammonia salts is of great significance for the organism, the total base being thus preserved. In contrast with the inorganic acids both the keto-acids and the lactic acid can be removed by combustion. While as far as the keto-acids are concerned this takes place through the action of insulin, the combustion of the other organic acids is independent of the presence of insulin. In all cases the combustion gives rise to the formation of carbon dioxide and water; the carbon dioxide thus produced is at once converted into bicarbonate. It is this reaction which causes the rise in the bicarbonate content of the plasma in an effective insulin treatment of diabetic coma.

As in the other severe forms of acidosis, uremia is frequently observed in diabetic coma, a fact which in Denmark was first pointed out by Warburg[225]. Besides the usual causes of uremia in acidosis (destruction of the tissue cells owing to acidosis and dehydration, oliguria due to dehydration, and circulatory disturbances) there is often in diabetic comatose conditions a severe lesion of the kidneys with considerable histological changes of the renal tissue (Kraus and Selye[107]). While in numerous severe forms of acidosis a reduction of the renal function takes place without any appreciable injury to the renal parenchyma (see p. 27) in diabetic coma there is thus in addition often a real lesion of the kidneys the clinical symptoms of which are albuminuria, cylindruria, and hematuria. Frequently an even very considerable reduction of the power of concentration is observed (Bulger, Peters, Lee and Murphy[19]), the excreted urine being dilute[130] and only containing small amounts of nitrogenous substances, salts, and sugar.

In diabetic coma high degrees of acidosis with reduction of the bicarbonate concentration of the plasma to 4–5 millimols or less (see Case records Nos. 21, 22, 23, 24, 25) are quite frequently seen. Often, however, there is no complete correlation between the degree of acidosis and the clinical condition. Thus the author has several times encountered bicarbonate values of 7–8 millimols in adult diabetics without the general condition being appreciably affected. In other cases the patients are deeply comatose at values of 8–10 millimols.

The history of the recognition and treatment of diabetic acidosis is fascinating reading which cannot fail to impress the modern student who, through the contributions of a generation, can follow the gradual clearing up of the ketosis problem and the final success in the treatment of the disease.

The modern treatment of coma starts with Fagge's[45] use of the intravenous injection of a saline solution in diabetic coma, a treatment which must be supposed to be inspired by the results of O'Shaughnessy, Latta, and Lewins in the treatment of cholera*). In a paper in Guy's Hospital Reports from 1874, »A case of diabetic coma treated with partial suc-

*) »I suppose that the hypothesis upon which I acted was essentially similar to that which formed the basis of the like treatment in the collapse of cholera.«

cess by the injection of a saline solution into the blood«, Fagge calls attention to the part played by the dehydration in the clinical picture and further emphasises the resemblance between the conditions of collapse in this disease and in cholera.

The development of the acidosis problem in diabetes followed 9 years later (1883) with the publications of Stadelmann[202] in Königsberg, whose results in the years that followed quite overshadowed Fagge's contribution. In a paper in the Archiv für experimentelle Pathologie und Pharmakologie entitled »Über die Ursache der pathologischen Ammoniakausscheidung beim Diabetes mellitus und des Coma diabeticum« Stadelmann points out the similarity between the clinical manifestations in diabetic coma and the symptoms in experimental acid poisoning described by Walter[224] in 1877. Notably the occurrence in both affections of the deep and rapid respiration which a few years previously had been characterised by Kussmaul[108] as »grosse Athmung« seemed striking to Stadelmann. A further very essential support favouring the assumption of an acid poisoning in diabetic coma was found by Stadelmann in the demonstration of large amounts of an abnormal acid in the urine of comatose patients, an acid which was identified by Minkowski[140] in 1884 as β-hydroxybutyric acid.

As a rational treatment of this acid poisoning Stadelmann, already in his first publication, suggested the direct injection into the blood stream of a 2–3 p. c. sodium carbonate solution. Since Stadelmann was thus the first to propose the use of unmixed alkali solutions in acidosis he may with some justice be called the founder of the intravenous alkali therapy. The first carbon dioxide analyses for the demonstration of acidotic changes in the blood followed a few years later (Minkowski[147] 1888).

During the next 25 years there was a lively interest in the treatment of diabetic coma with sodium bicarbonate (and sodium carbonate), the clinicians being evidently attracted by this theoretically rational therapy. Leading physicians[146] agreed that the alkali treatment was of great prophylactic value, for by oral ingestion of sodium bicarbonate in daily doses of 10–40 g a considerable reduction in the number of coma cases occurred. The intravenous treatment of the fully developed diabetic coma, on the other hand, proved disappointing, since in the course af a quarter of a century

hardly 10 people were saved from death by this treatment (Hanssen[62]). Even though the final result of the treatment was thus unsatisfactory the immediate effect of the intravenous injection of bicarbonate was often so dramatic that this is expressed in emphatic terms. Thus Rosenstein[184] (1890) describes the effect as »zauberhaft« and von Noorden[152] (1912) writes »Der Erfolg ist manchmal erstaunlich. Die Patienten, die schon vollkommen bewusstlos sind, wachen schon nach den ersten 300–400 cm^3 Infusionslösung aus dem Coma auf ...« It was probably this convincing immediate effect of the treatment which caused the unfailing interest in the intravenous treatment, but the few recoveries from a usually hopeless condition no doubt also made a strong impression on the physicians of that period. From his clinic Naunyn[62] could report the recovery of 5 comatose children by bicarbonate therapy, and Minkowski[146], Magnus Levy[62], Lüthje[124] and Lepine[228] each recorded recovery of an adult. Finally Grube[57] in 1904 could report »Über einen durch innerliche Darreichung grosser Mengen doppelt kohlensauren Natrons geheilten Fall von echtem diabetischem Coma«. Unfortunately, even though the coma was relieved, there was in all the cases a recurrence with fatal outcome in the course of at most a couple of months (Falta[46])*).

The first Scandinavian case of diabetic coma relieved by injection of sodium bicarbonate was reported by Hanssen[62] in 1910 in Norsk Magazin for Lægevidenskaben. The full record of this carefully observed and treated patient is given below (Case record No. 18). In 8 other cases treated at the Rigshospital in Kristiania only a slight transitory or no effect was obtained. The intravenous bicarbonate treatment of diabetic coma was introduced almost simultaneously in Denmark by Lauritzen[113], who, however, only saw a brief effect of the therapy. He used a 3–5 p. c. sodium bicarbonate solution, giving in all 25 g of sodium bicarbonate.

In estimating the results obtained in fully developed diabetic coma it is necessary to call attention to two facts which must be supposed to have been concurrent causes of the small number of lives saved. One of these facts, which rendered the treatment difficult, was the necessity of administering very large amounts of bicarbonate to relieve the acidosis,

*) In a case later reported by Labbé and Carrié[111] (1911) the improvement was of longer duration (see Case record No. 19).

since the alkali therapy was not then as now supplemented by the administration of insulin. Often several hundred grammes of sodium bicarbonate were administered; thus in the case treated by Hanssen which terminated in recovery, 660 g were given in the course of 4 days.

The second fact was the lack of understanding of the significance of the dehydration, manifested by the use of highly concentrated alkali solutions (3–8 p. c. sodium bicarbonate or sodium carbonate) a fact which, as previously mentioned in our account of the combating of acidosis in infantile diarrhea, was also conspicuous at the introduction of the alkali treatment of this disease 30 years later. Fagge's observations and considerations on the part played by the dehydration in the pathogenesis of diabetic coma had, as previously stated, been forgotten owing to the interest taken in the combating of the acidosis. As will appear from Rosenstein's and von Noorden's reports, a considerable effect on consciousness and respiration was attained by the injection of the concentrated alkali solutions; as the dehydration and the condition of shock still persisted, the improvement, however, was usually only temporary.

In the next decade (1910–1920) the value of the alkali therapy was constantly discussed. At the Rockefeller Institute in New York[4, 207], where the interest in the treatment of acidosis was especially marked, the oral bicarbonate therapy was developed to such a degree of perfection that recovery of numerous precomatose diabetic cases was achieved; by the administration of copious amounts of fluid the dehydration was simultaneously relieved. The alkali therapy did not, however, meet with unanimous approval among American clinicians, thus Joslin gave up this treatment already in 1917 and several American physicians followed this example under the influence of his authority.

After the introduction of the insulin therapy in 1922 the interest in the intravenous bicarbonate therapy rapidly declined, but it must be noted that at intervals of several years there are still clinicians who emphasise the life-saving value of the intravenous bicarbonate treatment. Thus in 1926 Meyer-Bisch[138] at Göttingen published 4 cases of diabetic coma, cured by intravenous injection of a 2.5 p. c. sodium bicarbonate solution after a previous insulin treatment had proved ineffective in relieving the comatose condition. In one of these patients there had been hypoglycemia with convulsions owing

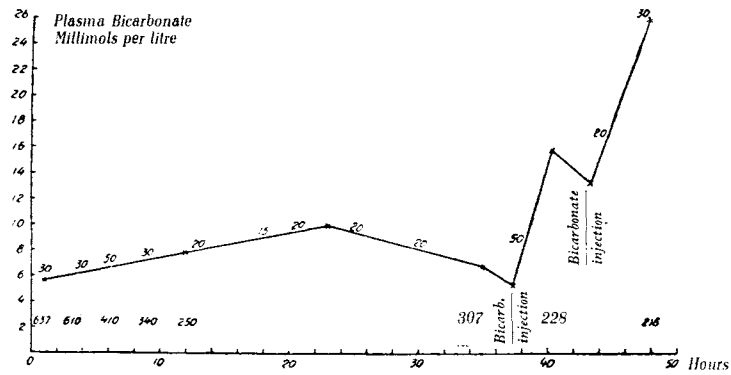

Fig. 10. Bicarbonate treated case of diabetic coma with insufficient insulin effect.

In spite of the administration of 235 international units of insulin during the first 36 hours of treatment no relief of the acidosis was obtained. Following intravenous injection of sodium bicarbonate solution a rapid rise in the bicarbonate concentration of plasma to normal values took place.

The administered insulin doses are entered above the bicarbonate curve.The numbers below the curve represent the blood sugar concentration expressed in mg per cent.

After Kahn, S., and Olmsted, W., J. Metabol. Research, 7-8: 29, 1925-26.

to the administration of insulin which had proved ineffective in relieving the coma; following the bicarbonate injection the patient at once recovered consciousness. The continued favourable results in Meyer-Bisch's department are mentioned by Kühn and Witscher[109] in 1931 and by Raadt[172] in 1933. Raadt states that, owing to the combined insulin and bicarbonate therapy, not a single death from diabetic coma had occurred for years at the Dortmund Clinic, while at the same time he expresses his regret that the treatment seems to have become obsolete elsewhere.

In America Campbell[22] (1922) was the first to maintain, after the introduction of the insulin therapy, that the treatment ought to be supplemented by the administration of alkali; he pointed out that in this way a quicker relief of the dangerous comatose condition was possible, a standpoint supported by Starr and Fitz[205] (1924). A few years later (1925–26) Kahn and Olmsted[86] proved the necessity of injecting sodium bicarbonate intravenously in the cases in which dyspnea and acidosis persisted after more than 6 hours' energetic insulin

treatment. They called attention to the fact that often the bicarbonate content of the plasma did not rise following the administration of insulin, while after intravenous injection of bicarbonate a rise promptly set in. Such a case of coma is reproduced in Fig. 10 after Kahn and Olmsted's paper. In the patient under consideration a total of 235 international units of insulin had been given in the course of 36 hours without producing any improvement of the acidosis. After intravenous injection of bicarbonate, the bicarbonate value rapidly rose to the normal.

The bicarbonate therapy was further warmly supported by Hartmann in 1928. He especially brought into notice the fact that with the treatment of coma adopted by Joslin, using exclusively insulin, it would often take several days before the acidosis was relieved, while at the same time he pointed out the risk of this prolonged acidotic condition and the not inconsiderable mortality in Joslin's material (11 p. c.). For the treatment of the acidosis Hartmann used partly (1927–31) a 1.5 p. c. sodium bicarbonate solution, partly (after 1931) the racemic sodium lactate solution previously mentioned. The initial dose of bicarbonate did not exceed 0.5 g per kg of body weight; for sodium lactate the maximal dose was 1 g per kg of body weight. The value of the alkali therapy appears very clearly from a diagram published by Hartmann[68] (1935) which shows the much more speedy restoration of the bicarbonate values of the plasma with the insulin – alkali therapy than with the administration of insulin alone (see Fig. 11).

Even more convincing than the rise in the bicarbonate content of the plasma was the clinical effect of the alkali injection, more especially the effect on consciousness, and on the dyspnea, the tachycardia, and the turgidity of the skin. As expressed by Hartmann: »The speed of recovery during the first two hours is more directly proportional to the dose of bicarbonate than to the dose of insulin.« In Hartmann's opinion the advantage of the supplementary alkali treatment thus consisted precisely in the possibility of relieving the dangerous acidotic condition more promptly, for which reason he recommends this therapy as a routine treatment of diabetic coma. In a later publication[69] (1938) further favourable results are reported of the combined insulin and alkali therapy; of 55 cases of coma in children only 2 deaths occurred, corresponding to a mortality of 3.6 p. c..

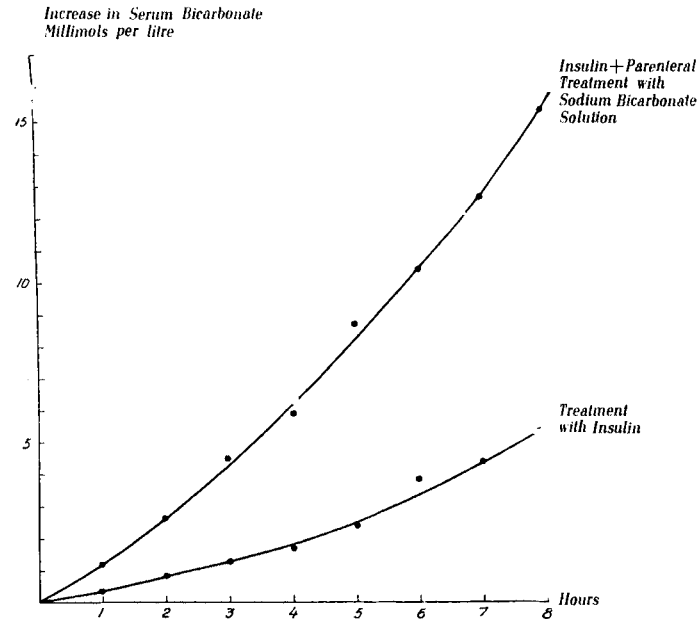

Fig. 11. Increase of the bicarbonate concentration of serum in diabetic coma during insulin treatment and following a combined insulin and bicarbonate administration.
The curves, which represent mean values, show the much quicker rise in the bicarbonate value obtained by supplementing the insulin therapy with administration of sodium bicarbonate.
After Hartmann, A., »Treatment of severe diabetic acidosis«. Arch. Int. Med., *56*: 413, 1935.

The combined insulin and alkali therapy was likewise recommended by Van Slyke[216] in 1934 in a lecture in the New York Academy of Medicine, and in 1936 by Conn[27], who more fully defines the indications for the use of alkali and speaks convincingly of the intravenous bicarbonate treatment in the following terms: »The response is frequently dramatic. Kussmaul's respirations change quickly to a normal type, and coma rapidly disappears«; and he adds ... »in a small group of cases in which the acidosis is severe and the coma has been prolonged, the administration of sodium bicarbonate may be and sometimes certainly is a lifesaving measure.« Conn used a concentrated (5–7.5 p. c.) sodium bicarbonate solution, but at the same time injected physiological saline subcutaneously for the treatment of the dehydration.

At the Mayo Clinic (Baker[9] 1938) the alkali therapy has been adopted in cases of severe dyspnea, in the presence of

a plasma bicarbonate concentration below 5 millimols and of persistent low plasma bicarbonate values, despite the attainment of normal blood sugar values by insulin treatment. Cullen[32] too (1936) states that he has used intravenous or subcutaneous injection of bicarbonate in diabetic coma and he thinks that in several cases the treatment was of decisive importance for the course taken by the disease. As stated on p. 73, he is of opinion that in severe cases of acidosis, the bicarbonate treatment is much more reliable in its effect than sodium lactate.

In Denmark the present author introduced the treatment of acidosis with isotonic sodium bicarbonate solution in 1934. The first treated case of coma dates from 1935. In publications from 1938[93] a detailed account has been given of the indications for the intravenous bicarbonate therapy, and it is pointed out that this treatment should be promptly adopted in all cases of diabetic coma in which the speedy supervention of death is to be feared, as well as in such cases in which the insulin treatment does not quickly bring about the desired improvement. In 1940 Krarup[106] reported a case of diabetic coma from Niels Steensens Hospital, Gentofte, in which the absence of an insulin effect seemed to be due to the loss of total base; after administration of isotonic sodium bicarbonate solution a considerable improvement of the condition set in, resulting in the recovery of the patient (Case record No. 23). In 1941 the author[99] documented the excellent effect of an intravenous bicarbonate treatment in a case of profound diabetic coma in a 63 year old woman, in whom the comatose condition and the acidosis were relieved exclusively by intravenous injection of isotonic sodium bicarbonate solution (Case record No. 25), and the same year he[100] reported 24 cases of coma treated successively without any deaths in the period October 1, 1939–April 1, 1941 (see p. 99). In the following 3 years (April 1, 1941–April 1, 1944) a total of 27 cases of diabetic coma was treated with only one death (see p. 99), a result equal to those attained by Hartmann with a combined insulin and sodium lactate treatment of diabetic coma in children (p. 93).

On surveying the recorded cases of diabetic coma in which insulin treatment has proved insufficient to relieve the comatose condition one will in some instances receive the impression that a better result could have been obtained if glucose had been administered at the same time (thus in one of

Meyer-Bisch's cases and perhaps in several of Hartmann's cases). To other cases this objection does not apply, the blood sugar being high enough to render probable the presence of a sufficient amount of sugar in the blood and tissues.

Against the background of the above it may be of value to sum up the possible causes of the occasional failure of insulin to relieve diabetic coma:

1. *The action of the insulin sets in too slowly,* so that the patient will succumb from acidosis before the effect of the insulin on the bicarbonate content of the organism is able to assert itself. While even in coma cases taking a favourable course it may often take several hours before a considerable increase in the bicarbonate content will occur as a result of the insulin treatment (see Fig. 11), *it is possible by intravenous administration of sodium bicarbonate solution to raise the concentration almost immediately above the values endangering life.*

2. *The effect of insulin is insufficient* even if the insulin is administered in large doses. The poor effect of the insulin may be due to the presence of the infection or intoxication which, (precisely as a result of the reduced insulin effect) has released the coma. Further it has been stated (Field[163]) that the insulin effect is less in the presence of severe acidosis, a fact which is important, since it is exactly in such cases that a strong insulin effect is required. In rare cases there may even be a complete resistance to insulin: such a case of coma, carefully examined, in which no improvement of the condition was obtained, either clinically or as evident from laboratory measurements, in spite of the administration of 1400 international units of insulin within a period of 30 hours, has been described by Thannhauser and Fuld[211].

In contrast herewith the bicarbonate effect is independent of the presence of infection, intoxication, and acidosis.

3. The acidosis is in part due, not to keto-acids, but to other organic acids (e. g. lactic acid) and inorganic acids. Thus Hartmann[66] has shown that in diabetic coma there may be an appreciable increase in the lactic acid content of the blood (up to 65 mg p. c., i. e. 7 millimols); similar values have been found by Meier and Thoenes[135]. Again, it is probable that in the presence of complicating renal lesions there is, as in other renal forms of uremia, a retention of inorganic acids in the blood, but these facts are but little investigated. Finally it is natural to suppose that the same factors which are active

in the development of the agonal acidosis (chiefly an accumulation of organic acids) also assert themselves in advanced cases of diabetic coma (Kirk[101]).

It is understandable that the administration of insulin will be without any direct significance for the combustion or neutralisation of these acids, *while the bicarbonate effect is independent of the nature of the acids present.*

4. *The acidosis is in part due to bicarbonate reduction as a result of a loss of total base.* A reduction of the total base value in the serum is, as already stated, a frequent finding in diabetic coma and is predominantly due to the loss of cation in the urine on excretion of the keto-acids. A reduction in the total base content of the serum will, as previously mentioned, cause a corresponding reduction in the total content of acid (the total anion content), which will in the first place affect the bicarbonate ion, the concentration of which will be reduced. While the giving of insulin will have no direct influence on the reduction of the total base, *the administration of bicarbonate will promptly bring about a rise in the total base value and thus remove one of the causes of the acidosis.*

5. As briefly stated above, *the insulin effect is dependent on the presence of a fair amount of carbohydrate in the organism.* In a number of diabetics, especially those who have been treated for a long time with a diet poor in carbohydrates, and in whom the intake of food has been deficient prior to the onset of the coma owing to nausea and vomiting, the glycogen stores will be sparse and the production of carbohydrate will chiefly take place at the expense of the tissue protein. The insufficient amount of carbohydrate in the organism will manifest itself during the insulin treatment in the development of hypoglycemia at a time when the bicarbonate content of the plasma is still much reduced.

In contrast with the action of the insulin, the effect of the administration of bicarbonate is independent of the carbohydrate content of the organism.

From the above it will appear that the treatment with isotonic sodium bicarbonate solution in diabetic coma as a supplementary therapy to the insulin treatment is based on a rational theoretical foundation.

As an indication of how diabetic coma should be treated we may lay down the following rules. In most cases treatment with insulin will suffice. It is only in cases in which the

patient is moribund ,or the insulin therapy does not bring about a decisive clinical improvement within the first hours after the initial treatment, that a supplementary treatment with intravenous injection of bicarbonate is absolutely indicated (Kirk[93] 1938).

The reason why the author[100] has, nevertheless, in his Department introduced the combined insulin and bicarbonate therapy as *a routine treatment* is that in this way it is usually possible to relieve the comatose condition in the course of about an hour and, by promptly raising the bicarbonate values of the serum above the limit endangering life, to reduce the possibilities of complications. In view of the fact that there is quite frequently a serious cause of the onset of the comatose condition, the prompt treatment of the coma seems to be of essential importance.

The procedure in my Department in the treatment of comatose diabetics is as follows. Immediately after admission the blood sugar is determined colorimetrically. When this analysis has confirmed that the case is one of diabetic coma, 80–120 international insulin units are injected subcutaneously, and 1–2 litres of isotonic sodium bicarbonate solution intravenously. Prior to the injection of the bicarbonate solution a blood sample is taken through the same needle for the determination of the serum bicarbonate, serum chloride, and eventually blood urea. The result of the bicarbonate determination expresses with certainty the degree of the acidosis and is a guide to the requisite intensity of the treatment. If the chloride value is reduced there are grounds for the administration of a physiological saline solution. In the presence of blood sugar values below 250 mg p.c. a 5 p.c. glucose solution should further be injected subcutaneously or intravenously so as to render possible the administration of a larger dose of insulin and to diminish the destruction of tissue protein. The necessary analyses may be performed even by interns in a few minutes. Usually blood samples for determination of bicarbonate and blood sugar are taken again after 4–5 hours. These analyses are repeated the next day or more frequently, as the severity of the case requires.

In cases in which the patient seems moribund, 1–2 litres of isotonic sodium bicarbonate solution should be injected without delay, that is to say, without awaiting the result of the blood sugar or bicarbonate analysis. *Altogether,* (as

mentioned on p. 32), *in cases where the patient is very low, up to 2 litres of isotonic sodium bicarbonate solution may be injected intravenously without preceding analysis as a first treatment, with no risk of overdosing.*[100] The amount of bicarbonate administered will as a rule be sufficient to relieve the most serious clinical symptoms and restore the patient to consciousness. In private practice, too, where the patient's condition seems dangerous and the conveyance to and reception at a hospital department may be supposed to take much time, the author strongly recommends practitioners to give the first bicarbonate treatment and insulin injection in the patient's home, and afterwards transfer the patient to the hospital. For the use of practitioners the author, as stated on p. 31, has had ampoules made which contain 1 litre of isotonic sodium bicarbonate solution and can be directly fixed on to a rubber tube and injection needle. It is only necessary to heat the ampoule in warm water before use.

In the Medical Department of the Holstebro District Hospital in the period from October 1, 1939 to April 1, 1941, 24 cases of diabetic coma (13 adults and 11 children) were treated in succession without lethal outcome, 6 by the administration of insulin alone, and 18 by a combined insulin and bicarbonate therapy. The gravity of the cases may be characterised by the statement that the average value of the bicarbonate in the serum before the treatment was 7.9 millimols per litre, while the average blood sugar value was 410 mg p.c.. 4 of the cases were complicated by pneumonia, 2 by cavernous pulmonary tuberculosis not previously diagnosed, 3 by severe purulent infections. In the first 24 hours on the average 175 international units of insulin were administered (not counting a possible administration of insulin before admission), and in the cases treated with bicarbonate further 1.5 litres of isotonic sodium bicarbonate solution. In all cases the coma was relieved as a rule within 1 or 2 hours, and the regulation of the patients' diet (full diet without sugar, with 150—200 g of bread and 100 to 150 g of potatoes) and insulin dosage was accomplished without difficulty.

In the 3-year period from April 1, 1941 to April 1, 1944, 27 cases of coma were treated (20 adults and 7 children); in all instances both insulin and bicarbonate were given. Of the treated patients 1 adult died. The average value of the serum bicarbonate before treatment was 7.9 millimols per litre, the average blood sugar value was 432 mg p.c.. 6 of the patients, among these the case with a fatal outcome, were complicated with pneumonia, 3 with purulent infections. Thus apart from the larger number of adult patients in this group, the cases, both with respect to the laboratory findings and to complications, showed a great similarity to the group of

patients treated in the years 1939—1941. In the first 24 hours on an average 182 international units of insulin and 3.2 litres of isotonic sodium bicarbonate solution were given.

It should be noted that with the alkali treatment of diabetic coma there is a greater possibility of overdosing than in the treatment of other forms of acidosis, a fact which has often been pointed out by the opponents of the alkali therapy. This danger of alkalosis is due to the circumstance that with the lively combustion of the keto-acids under the influence of the insulin, bicarbonate is formed (see p. 87). It must be admitted that with a simultaneous insulin and bicarbonate treatment a mild alkalosis may sometimes be observed, but it does not give rise to any serious symptoms, and moreover it is possible by repeated bicarbonate analyses of the serum through variation of the insulin dosing to prevent an excessive increase of the bicarbonate values. As far as the author knows, no case has been reported in which the alkalosis has reached a dangerous degree. As Hartmann so clearly expresses it, »The danger of moderate alkalosis is overrated..... The essential point concerning the use of alkalies is that advantage may be taken of its effect in hastening recovery from acidosis without fear that a dangerous degree of alkalosis may develop if the proper precautions are taken.« It will be understood that in this form of acidosis Van Slyke's nomogram affords little guidance with respect to the dosing of bicarbonate since very often less alkali must be given than calculated from the nomogram, while in other instances a continued enormous production of keto-acids necessitates a much larger dose of bicarbonate than estimated from the first analysis. Hence in but few other forms of acidosis is the frequent determination of the bicarbonate content of the plasma as necessary as in the treatment of diabetic coma.

Case record No. 17. Diabetic coma.

(Rosenstein,[184] Berlin. klin. Wochenschr., 27: 289, 1890).

A farm labourer, aged 35, who had suffered from severe diabetes since 1884, was taken seriously ill on January 9, 1890 with pain in the abdomen and a temperature of 39.6°; at the same time there were repeated severe vomitings. In the course of the day the condition was aggravated. Next morning the patient became semiconscious and did not answer questions. The respiration was noisy and deep, 28-32.

On account of the very low condition it was decided to try intravenous alkali treatment, and 500 c.c. of a 4 p.c. sodium carbonate solution were therefore injected. The effect of the injection was dramatic (»zauberhaft«), the patient, who had been unconscious before the injection, waking up immediately after and answering questions correctly. At this stage he seemed quite clear and slightly euphoric.

In the course of the day, however, the condition again became worse and the patient died early the next morning.

Case record No. 18. Diabetic coma.

(Hanssen, O.[62]: »Et Tilfælde af Koma diabeticum med Udgang i Helbredelse. Rediciv 2½ Md. senere. Mors.« (A Case of Diabetic Coma terminating in Recovery. Recurrence 2½ months later. Death). Norsk mag. f. lægevidensk., 74: 25, 1910).

A mechanic, aged 27, was admitted to the Rigshospital, Kristiania, on December 9, 1908. He had been well until August 1908, when he began to suffer from thirst and increasing fatigue. Polyuria further setting in, he consulted a physician but did not keep to the prescribed diet. As the condition did not improve, and he lost 14 kg in 3 months (68—54 kg) he was admitted to the Rigshospital.

In the physical examination following admission appreciable emaciation was observed, but otherwise nothing out of the ordinary. The urine contained 6 p.c. of sugar but no keton bodies. A low carbohydrate diet was prescribed on which he felt well, and during which treatment the weight in the months that followed rose to 66 kg.

At the beginning of June 1909 (i.e. after about 6 months' stay at the hospital), the condition was somewhat less satisfactory, the weight decreasing again. The urine showed a strong reaction for keton bodies and there was transient albuminuria. On June 22 the patient complained of a cold in the head and was disinclined to get up. In the evening the temperature had risen to 38.3°. In the course of the night dyspnea set in, and the next morning the patient was found collapsed with cold extremities and pronounced »grosse Athmung«. The breath smelled strongly of acetone, the pulse was small and rapid, 130. There was pronounced dullness and the patient complained of great fatigue and sleepiness.

In the morning 1 litre of 4 p.c. sodium bicarbonate solution was at once injected intravenously. The treatment was repeated at 5 p.m. with 1 litre, at 8 p.m. with 2 litres, and the next morning (June 23) again with 2 litres. *Thus in the course of 24 hours altogether 6 litres of fluid with a bicarbonate content of 240 g were injected;* in addition 90 g of sodium bicarbonate were given by mouth in a single dose. Further the patient was given copious amounts of milk, gruel, water and mineral water.

After each bicarbonate injection the patient stated that he breathed more easily and the bodily fatigue was less. The urine, in spite of the enormous amount of bicarbonate administered, still remained acid.

In the night between June 23 and 24 the patient slept well and had a good appetite next morning. The respiration was now 16, not audible, the pulse strong, 96. During the succeeding days the bicarbonate injections were continued in such large doses that in the first four days after the onset of the coma a total of 660 g of sodium bicarbonate was given. In the same period 680 grammes of acetone bodies had been excreted with the urine, calculated as β-hydroxybutyric acid. None of the portions of urine collected showed a neutral or alkaline reaction. Apart from the development of an erysipelas - like affection at the place of injection in the cubital vein, the further course of the disease was uneventful, and after July 11 the patient was able to be out of bed.

Though a daily dose of 70 g of sodium bicarbonate was given by mouth in the weeks that followed, the urine did not become neutral. On August 30, following otitis a comatose condition again developed. This time it was not found possible to relieve the coma by treatment with alkali and the patient died on September 6. After death a number of bicarbonate powders were found in the bed the patient having evidently been unable to take them.

Case record No. 19. Diabetic coma.

(Labbé, M. and Carrié P.,[111] *»Coma diabétique guéri par les injections intraveineuses de bicarbonate de soude«, Bull. et mém. Soc. méd. d. hôp. de Paris,* 31: *699, 1911).*

The patient was a woman, aged 65, who on November 16, 1910 was admitted to La Maison de Santé in Paris for cystitis. It was stated that for many years her weight had been excessive and since the age of 55 she had had symptoms of diabetes, but had never undergone any dietary treatment.

After admission, treatment with urotropine and bladder lavage was instituted, while a milk diet and 40 g of sodium bicarbonate were given daily by mouth on account of the diabetes. In spite of the treatment pyelonephritis developed with a temperature of 40°. Following a rise in temperature with chills a considerable exacerbation of the disease occurred on November 28, the patient became somnolent and could only with difficulty be made to answer questions. On the following day (November 29) she became unconscious with pronounced symptoms of diabetic coma.

In the course of the day 500 c.c. of 3 p.c. sodium bicarbonate solution were injected intravenously, after which the condition improved so much that the patient could take 60 g of sodium

bicarbonate by mouth. On November 30 she was wide awake and able to answer questions naturally. Both on that day and the three following days (December 1, 2, and 3) the intravenous and peroral bicarbonate administration was repeated, the improvement continuing during this treatment. On December 4 the bicarbonate injection was discontinued; already on the following day a comatose condition had again developed which was again successfully relieved by intravenous injection of 1 litre of 3 p.c. sodium bicarbonate solution. After another injection on December 5 (600 c.c. of 3 p.c. solution) the condition no longer gave cause for anxiety. The patient was discharged quite well on May 15, 1911.

The further course of the disease was remarkable by the fact that as late as 5 months after the discharge there had been no recurrence of the coma.

Case record No. 20. Diabetic coma.

(Marchand, F.,[127] München. med. Wchnschr., 59: *178, 1912).*

A man, aged 31, who had been suffering from diabetes since 1900 was admitted to the Medical Clinic at Heidelberg on December 7, 1910. The disease had shown signs of a steady aggravation during the last three years.

The day after admission (December 8) there were numerous vomitings and diarrheas as well as symptoms of incipient coma. The following morning (December 9) the respiration was rapid and deep, 36, and there was a distinct smell of acetone. At this stage the patient was somnolent, but was still able to answer repeated questions correctly. As the condition continually became worse, 100 c.c. of 5 p.c. sodium carbonate solution were injected intravenously at noon. After the injection the breathing was less laboured and slower, 24-28. As the patient was still somnolent, however, 200 c.c. of 5 p.c. sodium carbonate solution were again injected intravenously at 2 p.m.. *In the course of the following hour the respiration became quite normal (16-18) and the patient quite conscious.*

During the succeeding hours 100 g of sodium bicarbonate were given by mouth. After this the mental condition remained natural, and on December 12, the patient could be presented at a clinical lecture as relieved of an incipient diabetic coma.

Case record No. 21. Diabetic coma.

(Own observation,[93] Ugesk. f. Læger, 100: *977, 1938; Lancet* 236: *505, 1939).*

A draughtswoman, aged 27, who had suffered from diabetes for 5 years, and ever since the discovery of the disease had had dietary

treatment and received insulin was admitted to the Medical Department B of the Rigshospital, Copenhagen, on April 18, 1937.

She had felt well until April 10 when following the development of a purulent affection of the nose the condition had suddenly become aggravated, after which she reduced her insulin dose of her own accord. In the course of the succeeding days the condition grew more serious and on the morning of April 18 the patient was precomatose. Not until this stage was the patient's physician called in; he at once (at 10 a.m.) gave 80 international units of insulin. As there was no sign of improvement in the following hours, the patient was admitted to the Rigshospital at 3 p.m..

Immediately after admission 80 international units of insulin and 1 litre of saline were given subcutaneously, besides copious amounts of milk and mineral water. In spite of this the patient became less conscious in the following hours and at last was quite unconscious. Analysis of the blood made at 6 p.m. showed the presence of severe acidosis (5.5 millimols) whereupon, at 6.30 p.m. 2 litres of isotonic sodium bicarbonate solution were given intravenously.

During the injection the patient became fully conscious and answered questions correctly and naturally. In the course of the night 160 international insulin units were further given, and a glucose solution rectally. No further signs of clouded consciousness were observed. The blood urea concentration which had been greatly increased at the admission (178 mg p.c.) fell to normal values in the course of the following days. The patient was discharged well 1 month after admission.

Case record No. 22. Diabetic coma.

(Own observation, Ugesk. f. Læger,[93] 100: *977, 1938; Lancet* 236: *505, 1939).*

A retailer, aged 56, was admitted to the Medical Department B of the Rigshospital, Copenhagen, on May 21, 1938. He had suffered from diabetes for 7 years but in spite of the physician's advice had never followed any diet or had insulin treatment. There had not previously been attacks of coma. On May 15 he caught an infection with high fever, a cough, and angina. In the succeeding days the condition was gradually exacerbated, and when the physician was called in on the day of admission he was semi-conscious and delirious. Upon admission he was however able to give fairly accurate information about his condition. There was pronounced dyspnea and a distinct smell of acetone. Upon stethoscopy of the lungs numerous moist rales were heard in the right infrascapular region. The blood sugar concentration had risen to 490 mg p.c. and analysis of the plasma revealed a severe acidosis (9.4 millimols).

Shortly after admission (at 8.45 p.m.) 120 international units of insulin were given, besides (at 9—9.30 p.m.) 1 litre of saline sub-

cutaneously and plenty of soda water and milk to drink. In spite of this treatment the condition was however aggravated in the following hours, the patient did not answer when addressed, the respiration became stertorous, at times of the Cheyne-Stokes type, the colour of the skin was greyish, the eyes dim and sunken. A blood sample was therefore taken again (at 10 p.m.) for determination of the sugar and bicarbonate value. The results of the laboratory analyses also showed that the condition was aggravated, the blood sugar value having risen to 575 mg p.c. while the acidosis had further increased (5.6 millimols).

On account of the very low condition of the patient it was not considered advisable to wait any longer for the effect of the insulin to take place and at 11-12 p.m.. 2 litres of isotonic sodium bicarbonate solution were therefore injected intravenously. Already after the injection of 650 c.c. of the solution the patient woke from the comatose condition, answered questions naturally and spoke of his own accord to his relatives who had been summoned. At the same time the respiration, which before the bicarbonate injection had been audible at a distance became natural in depth and strength, but was still somewhat rapid. After the bicarbonate injection was finished the condition became still further improved and the patient now began to cough up large amounts of mucopurulent expectorate. Repeated analysis of the blood (at 1 a.m.) showed a blood sugar concentration of 400 mg p.c. and a rise of the bicarbonate value to 17.6 millimols. As the blood sugar concentration was still very high, 120 international units of insulin were again given (at 3 a.m.) with the result that the next morning the acidosis was completely relieved (24.4 millimols) and the blood sugar concentration was normal, 118 mg p.c.. During the entire comatose condition the diuresis had been plentiful and the blood urea only moderately increased (65 mg p.c.).

In the weeks that followed the patient continued to cough up large amounts of expectorate which upon analysis proved to contain pneumococci of type 7. Fluoroscopic examination revealed a massive infiltration of the whole lower right pulmonary lobe. About 10 days after admission pneumonia developed on the opposite side, but in spite of these complications the general condition was not much affected. Regulation of the diet and insulin dosage caused no difficulty, and the patient was discharged quite well on June 25.

The case record that follows illustrates a case of diabetic coma in which the administration of insulin, physiological saline, and glucose solution proved ineffective in relieving the acidosis. Uremia developed with threatening anuria. After treatment with isotonic sodium bicarbonate solution there was an increase of diuresis and an improvement in the general condition.

Case record No. 23. Diabetic coma.

(Krarup, N.,[106] Ugesk. f. Læger, 102: 27, 1940).

A woman, aged 57, who had suffered from diabetes for three years was admitted to the Niels Steensen Hospital, Gentofte, in 1938. After the discovery of the disease she had for a short time followed a diet, but had otherwise managed without consulting a physician. She had never been treated with insulin.

The last few days before admission she had had a cold but had been out of bed and about. On the day of admission, her daughter when talking to her mother on the phone had noticed that there was something peculiar about her and that the respiration seemed remarkably deep. She therefore called in a physician who at 3 p.m. found the patient lying on the floor in a fully developed coma.

When admitted to the hospital at 5 p.m. the patient was quite unconscious, cyanotic, cold and dehydrated, with a strong smell of acetone and deep respiration. The temperature was 35.6°, the pulse 88, regular and strong. Analysis of the blood revealed the presence of severe acidosis (5.0 millimols) and an increase in the blood sugar to 556 mg p.c.. The blood urea concentration was normal, 27 mg p.c., the urine contained sugar and acetone bodies, as well as leucocytes and casts.

In the course of the evening 320 international units of insulin were given in doses of 40 and 80 units partly subcutaneously, partly intravenously, further saline subcutaneously and intravenously 4 litres in all, and 1 litre of 5 p.c. glucose solution subcutaneously. At 10.30 p.m. (about 5 hours after admission) the patient began to answer when addressed, and later on could drink without aid.

The following day the condition was much improved, the patient was, however, very low, but at this stage could recognise her children. The urine still contained albumen, acetone bodies and sugar, the bicarbonate content of the plasma had risen to 12.2 millimols, the blood urea concentration to 64 mg p.c.. In the course of the day the blood sugar varied between 300 and 100 mg p.c.. The temperature was slightly increased, 37.8°—38°, the pulse was about 100.

On this day a total of 148 international units of insulin was given, besides 1 litre of saline and 1 litre of 5 p.c. glucose solution subcutaneously. She drank well over 1 litre of liquid and passed about 800 c.c. of urine, which only contained 0.75 g of ammonia.

On the third day of illness the turgidity of the skin had improved and the cyanosis had disappeared, but the general condition was not yet satisfactory, the patient being remarkably languid and semi-conscious. Analysis of the blood showed that in spite of the energetic treatment with saline there had been no further improvement in the acidosis, the bicarbonate content being 10.8 millimols. The plasma chloride value was normal, 111 millimols, the blood sugar con-

centration only slightly increased (100—200 mg p.c.), the blood urea value was increasing, 77 mg p.c.. *In the course of the day only 30 c.c. of urine was excreted* (collected by catheterisation). The urine contained albumen and sugar *but no keton bodies.*

As the patient no longer excreted keton bodies in the urine, and the bicarbonate content of the plasma was decreasing, while the blood urea concentration was increasing and anuria threatened, it was decided to try treatment with alkali, *and for the next three days a daily injection of 1 litre of 1.3 p.c. sodium bicarbonate solution was given intravenously. The patient improved distinctly after the bicarbonate treatment, the diuresis increasing greatly.* The blood urea concentration still rose for some days (to about 165 mg p.c.) and then decreased again. After the third injection the acidosis was relieved (20.8 millimols). 18 days after admission the albuminuria had subsided and the patient was discharged quite well, about 1 month after the beginning of the coma, on a well regulated diet and insulin dose.

The next case record shows an instance of diabetic coma in a child, with development of extreme acidosis in spite of such intense insulin treatment that pronounced hypoglycemia set in. *The observed bicarbonate value in the serum was the lowest ever reported in the literature.* Following administration of isotonic sodium bicarbonate solution the condition improved appreciably, simultaneously with the relief of the dangerous acidotic condition.

Case record No. 24. Diabetic coma.

(Own observation.[102] *The Danish Pediatric Society, 203. meeting, October 29, 1941).*

A girl, aged 5, from a provincial town of Sealand was admitted to the Pediatric Department of the Rigshospital, Copenhagen, on April 14, 1939. She had been suffering from diabetes for well over a year and in April-May 1938 had been admitted to the Department where a diet was instituted and 12 international units of insulin retard prescribed. For the past year she had been well except for a couple of periods with colds, in which she had been very low and on which occasions the parents had noticed deep respiration. Each time she had recovered spontaneously without any change in the insulin dose.

On April 13, the child was taken ill with a sore throat. In the course of the day she took hardly any nourishment, so the parents did not give her insulin. On the following night »grosse Athmung« occurred and the child became semi-conscious; no vomiting or diarrhea occurred.

On April 14, the parents called in the child's physician. At this stage she was semi-conscious but could still be roused. As the condition seemed dangerous, the patient was conveyed to Copenhagen in an ambulance. No insulin was given before admission.

When admitted to the hospital at 12.30 p.m. the child was precomatose, but could drink and ask for soda water. There was typical Kussmaul respiration with a frequency of 42, and a pronounced smell of acetone. The pulse was small, 138, the temperature 37.6°. The pupils reacted slowly, and the eye balls were now and then turned upward. The lips and tongue were dry, there was swelling and redness of the tonsils. Otherwise the physical examination showed nothing out of the ordinary except the absence of patellar reflexes. The urine contained large amounts of sugar and keton bodies. The blood sugar had increased to 406 mg p.c.

At 1 p.m. 20 international units of insulin were administered. One hour later, at 2 p.m. the child was mostly less alert, so 20 international units of insulin were again injected subcutaneously and 750 c.c. of saline subcutaneously.

At 4.30 p.m. the bicarbonate was determined on blood from the ear lobe. The analysis showed the presence of extreme acidosis with a serum bicarbonate value of 1.3 millimols (i.e. a reduction to about 1/20 of the normal value). At this stage the condition was critical, the patient being almost unconscious, the colour of the skin greyish, and the respiration very rapid, 46. So at 6—7 p.m. 650 c.c. of sodium bicarbonate solution were injected intravenously. Following the injection an appreciable improvement of the condition set in, the colour of the face became more natural with redness of the cheeks, and drops of perspiration on the skin while at the same time the respiration grew less deep. After completion of the treatment the child could be roused and answered some questions.

The analyses of the blood made at 7.20 and 10.30 p.m. revealed an increase in the bicarbonate value of the serum to 8.1 and 11.1 millimols, so that the child could now be supposed to be out of danger. Determinations of the blood sugar made at the same time showed that during the insulin treatment a severe hypoglycemia had developed. The blood sugar which, as already mentioned, had been much increased at the admission was 220 mg p.c. at 4.30 p.m., 160 mg p.c. at 6 p.m., 50 mg p.c. at 7.20 p.m. and 25 mg p.c. at 11 p.m. Corresponding to this the urine was free from sugar at 7.20 p.m., but contained large amounts of keto-acids, a further indication that in spite of energetic insulin treatment it had not been possible to relieve the acidosis. In order to relieve the hypoglycemia the child was given tea to drink with plenty of sugar.

At 2 a.m. on April 15 the bicarbonate concentration had increased to 15.6 millimols and the blood sugar to 150 mg p.c. The child coughed somewhat during the night but otherwise felt well and drank some milk and water. At 6 a.m. 12 international units of

insulin retard were injected. At 9 a.m. the child was perfectly alert, but the respiration was still deep with a faint smell of acetone. The tongue was moist, not coated. The temperature was 38.2°, the pulse 120. The urine contained sugar, keto-acids and albumen. In the course of the day the child grew still more alert, drank plenty of milk, and ate a good many biscuits. At 5.30 p.m., 24 hours after extreme reduction of the bicarbonate concentration had been demonstrated, another analysis of the blood *showed that the acidosis was now relieved* (23.6 millimols).

The next day, April 16th, a purulent discharge from the right ear was observed and otoscopy showed the presence of an acute otitis media.

The further course was uncomplicated. The ketonuria disappeared on April 20. On May 9, the child was allowed to get up. She was put on a suitable diet with 28 international units retard and gained 2 kg in weight during her stay. She was discharged quite well on the 21. May.

The last case record shows an instance of diabetic coma in a woman, aged 63, with cavernous pulmonary tuberculosis in whom the comatose condition was relieved in the course of 2 hours *exclusively by intravenous injection of isotonic sodium bicarbonate solution.* (It should be noted that during this observation period we were ready to give insulin at the first sign of the treatment being ineffective).

Case record No. 25. Diabetic coma.

(Own observation,[99] *Nord. med.,* 11: *2279, 1941).*

The patient was a widow, aged 63, from a neighbouring town, who was admitted to the Medical Department of the Holstebro District Hospital on December 28, 1940, at 9.30 p.m. in a comatose condition.

She was stated to have been well until 10 years ago when diabetes mellitus was diagnosed. Following the diagnosis of the disease she was hospitalised and put on a diet which however she did not follow. 5 years ago she was again sent to hospital and dieted. After this second stay at the hospital the patient had not followed the prescribed diet, but had eaten the same food as the rest of the family. During the last 3 years especially she had rapidly lost weight, but had otherwise felt well.

On the morning of December 24 the patient felt a cold coming on, and coughed a little. She looked very sleepy on Christmas Eve but was mentally alert. The next day (Dec. 25) she felt tired and sleepy, still she paid some Christmas visits in Holstebro. On December 26, she felt somewhat better, but on the day before admission the patient again began to get somnolent, and the condi-

tion was gradually aggravated until at 6 p.m. on the day of admission she was semi-conscious and unable to recognise those around her. In the afternoon there had been brownish vomiting but no other gastro-intestinal symptoms.

It should be noted that the patient had never been treated with insulin and that, especially, no insulin had been given before admission to the hospital.

Upon admission at 9.30 p.m. the patient was unable to recognise the relatives who accompanied her but answered questions put to her in a whisper (vox cholerica) with single words. Immediately after admission the condition was further aggravated, the patient becoming unconscious. There was pronounced Kussmaul respiration with a frequency of 32. The temperature was subnormal, 36°, the pulse 104. The tongue was quite dry with a large parchmentlike spot corresponding to the tip; the nose, tip of the tongue, and the peripheral parts of the extremities were chilly.

On stethoscopy of the lungs moist rales could be heard on the left side. The heart stethoscopy was natural. The rest of the examination showed nothing out of the ordinary except the absence of patellar reflexes.

At 10 p.m. a blood sample was taken which revealed the presence of a severe acidosis, the bicarbonate content of the serum being reduced to 4.9 millimols per litre. The serum chloride was 105 milliequivalents per litre, blood urea 59 mg p.c., blood sugar 510 mg p.c..

After obtaining the blood sample *4 litres of isotonic (1.3 p.c.) sodium bicarbonate solution were at once given intranvenously* (total injection 52 g of sodium bicarbonate), the first 2 litres being injected rapidly, the last 2 more slowly. Already after the injection of 1 litre the respiration grew less deep, but with unchanged frequency. The expression of the face now changed distinctly, becoming more natural, and the skin assuming a faint rosy tinge. After further injection the condition continued to improve. The patient began to cough, and distinct moist rales were heard, while at the same time the respiration grew more natural. Shortly after it was observed that the tongue had become moist and warmer, and the patient now replied to questions and was able to intonate naturally. After the injection of 3 litres the patient spoke of her own accord. After injection of 4 litres the respiration was almost natural and the patient was now able to sit up in bed and apparently with relish drink one or two cups of coffee unaided (see Fig. 12).

During the latter part of the bicarbonate injection the patient passed plenty of clear light-coloured acid urine containing sugar, acetoacetic acid, and acetone.

At 12.30, half an hour after cessation of treatment, a blood sample was again taken which showed an almost complete restitution of the bicarbonate content of the organism, the bicarbonate value being

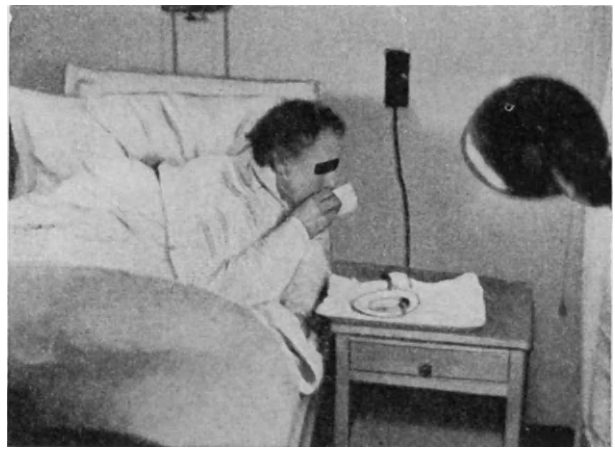

Fig. 12. The patient 2 hours after admission in diabetic coma, immediately after injection of 4 litres of isotonic sodium bicarbonate solution. No insulin injection had as yet been given at this stage, nor had the patient ever during a 10-year period of illness had any insulin.

19.5 millimols. The blood sugar was at this stage still high, 485 mg p.c.

Only when the comatose condition had been relieved was treatment with insulin initiated, 48 international units of insulin being given at 2.30 a.m.. At 6 a.m. the blood sugar had dropped to 250 mg p.c.. Another dose of 23 international insulin units was now given. A blood sample taken at 11 a.m. showed a normal bicarbonate value (21.6 millimols).

Fluoroscopic examination of the lungs the day after admission revealed a tuberculous affection of the whole left lung with formation of cavities and infiltration of the upper part of the right lung. The expectorate contained large amounts of tubercle bacilli.

The further course of the diabetes was uneventful. The patient was without difficulty put on a suitable diet. There was continued abundant expectoration, and on January 7, 1941 the patient was transferred to the Tuberculosis Department of the Hospital where death supervened 3 months later (April 14, 1941) without any previous comatose condition.

2. Ketonemic Vomiting in Children.

This affection, which occurs at the age of 2—10, manifests itself in periodically recurring fits of violent vomiting with a considerable effect on the general condition and an abun-

dant excretion of acetone, acetoacetic acid, and β-hydroxybutyric acid in the urine. That we are here concerned with a serious acid poisoning of the same kind as in diabetes was pointed out by Edsall[40] already in 1903. Later investigators have fully confirmed Edsall's observation. Thus it is common during the attacks to find an appreciable reduction of the bicarbonate content of the serum, a reduction which is chiefly due to an accumulation of keto-acids, the concentration of which may rise to 400 mg p.c.. However, in recent investigations it has been shown that there is also an accumulation of other organic acids, especially lactic acid (Darrow[163]). Considering the violence of the vomiting, which may involve a loss of fluid of up to 5 litres in 24 hours, it would be natural to suppose that the total base content of the serum would also often be reduced, but the few available investigations have not shown any total base reduction worth mentioning.[163]

The etiology of the disease has not yet been established, but it is probable that, as in diabetes, changes in the carbohydrate metabolism are of essential importance, possibly consisting in a reduced capacity of assimilating carbohydrate and intolerance to carbohydrate deficiency. In this affection it is comparatively rare to find clinical signs of acidosis (Strøm,[209] Klinke[104]), presumably because children are little affected by moderately severe reductions of the bicarbonate content of the organism. The reason why the acidosis does not usually develop to excessive degrees in spite of the considerable ketonemia is perhaps that the vomitings, which most frequently contain free hydrochloric acid, counteract the development of acidosis. It is beyond doubt, however, that in this affection too symptoms may be seen that greatly resemble the severest degrees of diabetic coma, thus symptoms of dehydration and collapse (sunken eyes, sharp nose, dry lips, dullness, somnolence, and loss of consciousness) as well as typical acidotic respiration, »grosse Athmung« (Pfaundler, Ström[209]). In the gravest cases the disease may have a fatal outcome.

In the treatment the administration of glucose in combination with insulin frequently seems to bring about a decisive improvement of the condition. In the severest cases with somnolence and pronounced clinical symptoms of acidosis the parenteral glucose treatment should be supplemented by intravenous injection of sodium bicarbonate solution so as to

relieve the critical condition more quickly. Alkali treatment of the grave forms of this disease seems so far only to have been tried by French clinicians, who have used a 4 p.c. sodium bicarbonate solution (Willemin-Clog[12]).

Case record No. 26. Ketonemic vomiting.

(Own observation).

A boy from South Jutland, aged 2½ years, was admitted to the Children's Department of the Rigshospital, Copenhagen, on April 13, 1938. In the course of the last six months he had had four attacks of vomiting accompanied by semi-consciousness and coma lasting a couple of days. Between the attacks the child had been bright and natural, but just before them he had been restless, cross, and irritable.

The last attack had begun with vomitings on the morning of the day of admission. Upon admission in the evening the child was tired and sleepy but gave sensible answers. The examination showed nothing special beyond the presence of acetone and acetoacetic acid in the urine, which did not contain sugar.

In the course of the following night the boy vomited once and on the morning of the 14th of April a distinct acetone odour of the respiration air was observed. At noon bicarbonate determination of the serum was made and showed the presence of a moderate acidosis (14.2 millimols). Later in the day there were several vomitings and at 6 p.m. in the evening the child was more dull and semiconscious with deep, not very rapid respiration. At about 10 p.m., however, the condition spontaneously improved somewhat, the boy becoming more alert and being able to take nourishment.

On the next day (April 15) the bicarbonate content of the serum had risen to 20.4 millimols. Acetone was now no longer found in all the portions of urine, and the child drank copiously but still vomited a few times. In the following days the condition further improved and the bicarbonate values rose continually (April 16, 22.7 millimols, April 17, 25.4 millimols). Apart from a small relapse following fluoroscopic examination the improvement continued and the child was discharged quite well on the 8th May.

3. Inanition Acidosis.

In complete inanition, acidosis regularly occurs, which like the diabetic acidosis is due to an abnormal production of keto-acids: acetoacetic acid, and β-hydroxybutyric acid. The causes of the formation of the keto-acids are the same as in

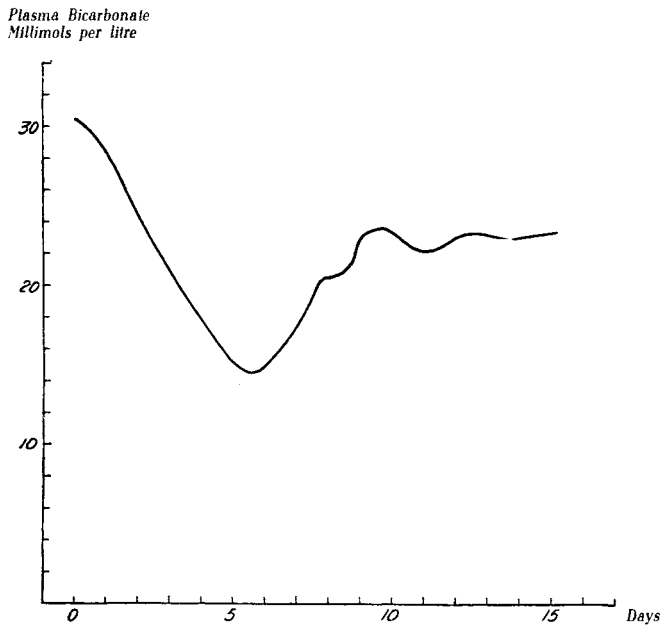

Fig. 13. The bicarbonate content of the plasma during inanition. After Lennox, W. G., O'Connor, M., and Bellinger M., »Chemical changes in the blood during fasting in the human subject«, Arch. Int. Med., *38:* 553, 1926.

diabetes, the production of acid being in both cases due to an imperfect carbohydrate metabolism in the organism. Inanition acidosis, however, does not attain the same severe degrees as diabetic acidosis, the power of carbohydrate combustion not being affected. During inanition no inconsiderable amounts of carbohydrate undergo combustion, carbohydrate being formed at the expense of the tissue protein, and for this reason it is rare to see any considerable reduction of the plasma bicarbonate values. Long investigation series by Lennox, O'Connor, and Bellinger[115] have shown that the plasma bicarbonate concentration will not usually fall below 16 to 18 millimols (see Fig. 13). The observed reduction seems to correspond closely to the increase of keto-acid in the blood.

While the occurrence of inanition as an independent disease is clinically rare, inanition occurs as a complication in numerous medical and surgical diseases which are accompanied by nausea and vomiting. For this reason inanition

ketonemia will frequently be a contributary cause of acidosis (see e.g. Case record No. 16).

While the treatment of diabetic coma in the first place requires the administration of insulin, this therapy is not needed in inanition acidosis, where the administration of carbohydrate alone is sufficient for the combustion of the keto-acids, the insulin production of the organism being normal. The carbohydrate is best given in the form of glucose, either parenterally (see p. 38) or rectally. The demonstration of ketonuria (or ketonemia) in cases of non-diabetic acidosis is an indication for such a glucose therapy.

4. Acidosis in Anoxemic Conditions

(Cardiac Decompensation, Peripheral circulatory Failure and Shock, Severe Anemias).

In conditions where owing to circulatory insufficiency an oxygen deficiency arises in the tissues the lactic acid will not undergo combustion in sufficient amount or be reconverted into glycogen; hence an accumulation of lactic acid in the organs and the blood will occur. While the lactic acid content of the blood is usually normal in compensated heart affections (20 mg p.c., 2 millimols), a distinct rise in the lactic acid concentration is frequently observed in cardiac decompensation (Meakins and Long,[132] Jervell[84]). The rise, however, is not a constant phenomenon (Bang[11]). Quite frequently the lactic acid increase runs fairly parallel to the degree of decompensation. Even in severe failure the concentration of lactic acid in the blood seldom rises above 40–50 mg p.c. (4–5 millimols) and the bicarbonate value of the plasma rarely falls below 17 millimols; the maximum lactic acid value observed by Jervell under these circumstances was 77 mg p.c., while Meakins and Long in an extremely exhausted patient with mitral stenosis found values over 100 mg p.c. (10 millimols). The observed values for this carefully studied patient are given in Table 5. It will be seen from the table that the most considerable rises in the lactic acid content of the blood occurred after such severe exacerbations of the clinical condition that the patient could almost be termed moribund. The condition thus forms a transition to the agonal acidosis described on p. 176.

Table 5.

Lactic acid content of the blood in a case of decompensated mitral stenosis.

After Meakins, J. and Long, C. N., »Oxygen consumption, oxygen debt and lactic acid in circulatory failure«, J. Clin. Invest. *4:* 273, 1927.

Date 1926	Lactic acid content of blood mg p.c.*)	Comments on clinical condition
7. January	35.8	Moderate decompensation
11. January	51.8	Increasing failure
15. January	29.8	General condition better
27. January	30.5	Pronounced dyspnea
28. January	110.0	Almost moribund
17. February	38.7	Considerable improvement
24. February	30.3	Condition unchanged
13. March	27.7	Increasing dyspnea
18. March	105.1	Moribund
25. March	49.8	Condition improved but patient very weak
26. March	40.3	Condition unchanged
27. March	108.5	Moribund, unconscious died 12 hours later.

Even though it has been surmised that the final cause of death in cardiac decompensation is the accumulation of lactic acid in the myocardium, it is not very probable that the condition in cardiac decompensation can be improved by the administration of alkali; the administration of large amounts of saline may even be expected to aggravate the disease. The rational treatment in the cardiac lactic acid acidosis is undoubtedly inhalation of oxygen, an increase of the oxygen content of the blood involving a livelier combustion and resynthesis of the lactic acid.

Besides the accumulation of lactic acid other factors often contribute to the development of acidosis in cardiac decompensation. Thus in investigations in the author's Hospital Department it has been shown (Fabricius-Hansen[43]) that in cardiac decompensation an increase in the sulphate and phosphate values of the plasma is frequently encountered. This increase in acid which usually occurs simultaneously with an increase in the blood urea value (cardiac uremia) is due to

*) Normal value with the method adopted 20-23 mg p.c.

a reduction of the renal function caused by the circulatory failure. From this it will be realised that the cardiac acidosis not rarely has a renal component. In this connection it should be noted that in chronic nephritis with uremia and acidosis the presence of myocardial lesions do not constitute an absolute contra-indication to the parenteral bicarbonate treatment (see Case record No. 30).

Of far greater practical importance is, in the author's opinion, that lactic acid acidosis which occurs in peripheral circulatory failure and shock. In the preceding chapters it has been mentioned that the peripheral anoxemia must be supposed to be an important contributory cause of the development of acidosis in cholera and infantile diarrhea, that is to say, in diseases in which on account of dehydration, shock, and intoxication, an often extreme peripheral circulatory failure has set in. Under such circumstances, when the heart it not, or only in slight degree, affected, the administration of bicarbonate solution is of the greatest value and will sometimes be life-saving, since both the acidosis, the state of shock, and the dehydration will thus be ameliorated. This question is treated thoroughly in connection with the discussion of the individual groups of diseases.

Finally it must be mentioned that in severe anemia acidosis may likewise occur (Whitney[231]); it must then be supposed to be of an anoxemic character. Thus Salvesen[188] found upon examination of a man aged 51 who was suffering from pernicious anemia that the bicarbonate content of the plasma had been reduced to 4.4 millimols 3 days before the supervention of death. The hemoglobin value was 15 p.c., the number of erythrocytes was 0.42 million. In the last days of the patient's life there was pronounced somnolence with deep and rapid respiration of Kussmaul's type.

5. Acidosis in Anesthesia.

The occurrence of acidosis in ether anesthesia was demonstrated as far back as 1918 by Henderson and Haggard,[72] and this finding has later been confirmed by several other investigators. Often the acidosis is only moderate but it may also attain considerable degrees, thus Van Slyke, Austin, and Cullen[218] found a reduction of 5–15 millimols in the bicarbonate content of the plasma during ether anesthesia. Investi-

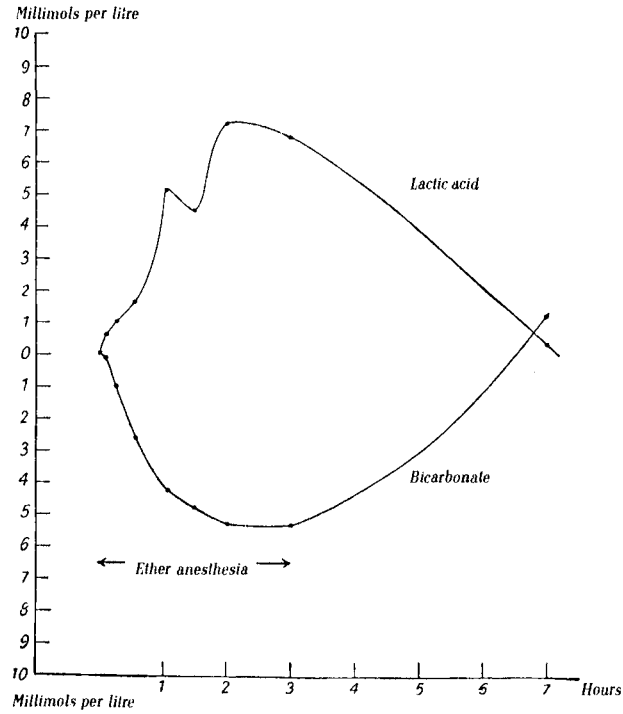

Fig. 14. Lactid acid increase and bicarbonate reduction in the plasma during ether anesthesia of a dog.

Constructed after Ronzoni, E., Koechig, I., and Eaton, E. P., »Rôle of lactic acid in the acidosis of ether anesthesia«, J. Biol. Chem., *61:* 465, 1924.

gations by Ronzoni, Koechig and Eaton[183] have proved that the acidosis is in the main due to an accumulation of lactic acid in the blood, and that the increase in lactic acid usually takes a course fairly parallel to the reduction of bicarbonate (see Fig. 14). The abnormal production of lactic acid is presumably in part a consequence of a reduction of the oxidation in the tissue cells[55,82] due to the anesthesia, whereas anoxemia does not seem to be of any great significance for the development of the lactic acid acidosis. It should further be stated that in most investigations no appreciable accumulation af keto-acids was found in the blood. It must be admitted, however, that the detailed mechanism which gives rise to the acidosis is still unknown.[145]

In some cases, possibly especially such as are connected with considerable motor unrest and resistance movements

during the initiation of the anesthesia, the acidosis seems to occur shortly after the beginning of the latter. After cessation of the anesthesia the bicarbonate value usually returns to normal in the course of 3–5 hours (see Fig. 14). On examination of 9 ether anesthetised patients Jacobsen[83] in 1943, in the Surgical Department of the Holstebro District Hospital, using Austin's gasometric technique, found a fall in the bicarbonate concentration of the serum amounting to 2.0–7.0 millimols; the average bicarbonate reduction was 4.2 millimols, the duration of the anesthesia was half an hour to two hours. The acidosis has been observed not only in ether and chloroform anesthesia (Wymer[233]) but also in narcylene, nitrous oxide, and ethylene anesthesia, though not as a constant phenomenon (Leake and Hertzman[114]).

Clinical investigations being as yet rather scarce, there is no possibility of estimating the practical significance of this form of acidosis. At the outset it may be anticipated that the injurious effect of the acidosis will especially assert itself in cases in which acidosis of another kind is present already before the operation. In general, human acidosis seems to reach less high degrees than in the animal experiments (Wymer[233]). A closer investigation of this form of acidosis with the available methods (total base determination, direct determination of individual organic acids etc.) may possibly furnish valuable information. In such researches it should be kept in mind that owing to the presence of ether in the blood a special technique must be adopted for the bicarbonate analysis (Austin[8]).

E. Acidosis as a Consequence of Inhibition of the Tissue Oxidation (Inhibition of the Intermediary Metabolism).

Lactic acid acidosis in experimental guanidine intoxication.

It has been shown in some of the preceding sections (see pp. 42 and 115) that with a deficient supply of oxygen to the tissues an acidosis will arise as a consequence of the accumulation of lactic acid. A similar increase of the lactic acid content of the tissues and the blood will, however, occur even though the supply of oxygen to the tissues be normal if the

oxidation processes in the tissues are inhibited so that the oxygen cannot be utilised by the cells. Such an inhibition of the oxidation in the tissues has been demonstrated experimentally on animals after injection of guanidine and guanidine compounds. Other oxidation-inhibiting substances are known (narcotics,[55, 82] arsenite,[82] cyanide[82]). Concerning conditions in ether and chloroform anesthetisation the reader is referred to the previous chapter; the rest of the oxidation-inhibiting substances will not be mentioned here, since, as far as the author knows, no investigations are available on the occurrence of acidosis in these intoxications.

A detailed account of the oxidation processes in the tissues (i. e. of the intermediary metabolism) does not come within the scope of this exposition. The tissue metabolism comprises numerous complicated chemical conversions which have as yet only been elucidated in their main features. We may, however, mention with reference to our present subject, the lactic acid acidosis in experimental guanidine poisoning, that the oxidation of lactic acid is assumed to take place by the separation of hydrogen from the lactic acid molecule; the separated hydrogen is carried on by means of a transport system to a combination with the free oxygen. If the hydrogen transport system is blocked by the effect of poisons, the lactic acid will not be dehydrogenated, (i. e. oxidised), which will cause an accumulation of lactic acid in the tissues and a consequent increase of the lactic acid concentration of the blood, i. e. a lactic acid acidosis. Such a poisonous effect is supposed to be exercised by guanidine, though in the author's opinion it has not yet been cleared up at what stage of the transport system the guanidine effect asserts itself.

The first investigations on acidosis in guanidine poisoning are derived from Watanabe[226] (1918) who demonstrated a reduction of the pH and carbon dioxide content of the blood in the experimental poisoning of animals. More thorough researches on the guanidine preparation Synthaline (decamethylenediguanidine) were published by Staub[206] in 1928. The investigations show that after injection of synthaline into rabbits in a 0.5 p. c. solution there occurs a reduction of the oxygen consumption of the animals measured by Krogh's metabolism apparatus. The maximum reduction of the oxygen intake observed amounted to half the original value; in experiments on 7 rabbits the average oxygen consumption was 0.60 litres per hour before the intoxication, after the

synthaline injection 0.40 litres per hour. In connection with the reduction of the metabolism there occurred a considerable rise in the lactic acid content of the organs of the animals.

In 1931, in experiments on dogs Minot,[141] in agreement with Staub's observations, was able to demonstrate a very considerable rise in the lactic acid concentration of the blood (up to 250 mg p. c.) after poisoning with guanidine. These experiments were continued in 1933 by Minot, Dodd and Saunders,[143] who besides a lactic acid analysis made a determination of the pH and bicarbonate content of the blood during intoxications. The investigations showed that after injection of 110–275 mg of guanidine hydrochloride per kg body weight there often developed a severe acidosis with reduction of the bicarbonate concentration of the blood to between 3 and 15 millimols. As in Minot's experiments, the lactic acid content of the blood was found to be much increased (88–201 mg p. c.). A couple of these experiments are quoted below.

Table 6.

Acidosis in Experimental Guanidine Intoxication of Dogs. After Minot, A. S., Dodd, K., and Saunders, J. M., J. Clin. Invest., *13:* 917, 1934.

	Date	pH	Bicarbonate millimols	Lactic acid mg p. c.	Guanidine mg p. c.
Experiment No. 1.					
Before inject. of guanidine	Oct. 30, 1933	7.35	22.8	21	0.48
After » »	Oct. 31, 1933 9 a. m.	7.21	15.6	61	
After » »	Oct. 31, 1933 2 p.m.	6.97	6.2	166	3.30
Experiment No. 2.					
Before inject. of guanidine	Nov. 1, 1933	7.37	23.6	19	0.38
After » »	Nov. 2, 1933	7.41	22.7	19	1.34
After » »	Nov. 3, 1933 9 a. m.	7.38	23.0	27	0.98
After » »	Nov. 3, 1933 4 p.m.	7.10	12.4	93	2.20

When discussing the acute gastroenteritis of children we mentioned (pp. 47 and 73) that in severe cases of this disease an increase of the guanidine values of the blood had often been found (Dodd, Minot, and Casparis,[37] Minot and Dodd[142]),

which may be supposed to be a contributory factor in the development of the acidosis. The action of bacterial poisons on the intermediary metabolism is perhaps also of etiological significance for the occurrence of acidosis in acute suppurative otitis media in infants (Hartmann;[65] Csapó and Kerpel-Fronius;[28] Kirk[103]) and in other dangerous infections (see p. 168 and 174). A closer investigation of these facts would no doubt be profitable.

F. Acidosis Due to Retention of Acid (and Loss of Total Base).

1. *Acute nephritis.* 2. *Nephritis in mercuric chloride poisoning.* 3. *Nephritis in the eclampsia of pregnancy.* 4. *Chronic nephritis.* 5. *Renal amyloidosis.* 6. *Prostatic hypertrophy.* 7. *Other surgical urinary diseases.*

In all serious renal diseases, both medical and surgical, acute and chronic, a severe acidosis will often occur. The essential condition for the development of the acidosis is the presence of a very considerable renal insufficiency; hence the acidosis is only found in renal diseases in which, as a sign of the renal insufficiency, there is also an increase of the blood urea and retention of nitrogen. While there is thus uremia in all cases of renal acidosis, cases of renal uremia are sometimes encountered in which there is no acidosis. On the other hand, the acidosis may in some instances of uremia reach just as severe degrees as in diabetic coma (reduction to 3 millimols) and may thus in itself constitute a grave danger to life. Even in a less pronounced acidosis the patients will, according to the author's experience ,as a rule appear more ill than in corresponding degrees of other forms of acidosis. Precisely because the acidosis is closely connected with the occurrence of renal insufficiency, and not with other special syndromes of renal disease, the acidosis will be fairly independent of the nature of the disease in question and will occur with essentially the same biochemical and clinical picture in the different renal affections. The acidosis of the various renal diseases will therefore be discussed in the same chapter.

The finding of acidosis in a renal disease is always a grave prognostic sign, but this fact should not, as the tendency has been, induce complete pessimism with respect to the

possibilities of treatment. Renal acidosis has especially been investigated in chronic medical nephritis, and it is no doubt this fact which has contributed to an unfortunate reserve in the use of bicarbonate treatment in renal forms of acidosis. *The author is anxious to point out that the demonstration of acidosis is only indicative of a hopeless prognosis if the principal disease in itself has a hopeless prognosis.* In the diseases in which recovery is not rare or excluded (acute nephritis, eclampsia of pregnancy, prostatic hypertrophy), the finding of uremia complicated with acidosis will, it is true, generally denote a graver prognosis than the finding of uremia without acidosis, but the realisation of the presence of the acidosis will, on the other hand, often afford a possibility of a more effective treatment and will thus improve the prognosis. In this connection it should be kept in mind that in such diseases, in spite of renal insufficiency, there will often be reparable renal changes. When the principal disease is relieved (with or without bicarbonate treatment) the acidosis will also be relieved. Both acute nephritis, eclampsia and prostatic hypertrophy may therefore, as far as the acidosis is concerned, in a way be compared to diseases such as gastroenteritis, bile fistulas, and the like, as in all these diseases there is a possibility that the acidosis may be relieved without any tendency to recurrence. Especially because of the fairly good prognosis in prostatic hypertrophy the combating of the renal acidosis in this disease will be of very great importance. The treatment of this form of acidosis has since the author's introduction of the parenteral bicarbonate therapy at Professor Abrahamsen's Department of the Bispebjerg Hospital in Copenhagen come to be fairly widely used in Denmark, but the consistent adoption of it in other hospital departments would, judging by the excellent results from the Bispebjerg Hospital, no doubt be life-saving in many cases.

That an acid poisoning is present in uremia was first pointed out by von Jaksch in 1888 on the basis of titrations of the alkali content of the blood. Von Jaksch, however, also found a reduced alkali content in diseases where later investigators have failed to demonstrate the presence of acidosis, hence his results have been subjected to criticism. The first who, using a modern technique demonstrated a reduced carbon dioxide content in the alveolar air in renal insufficiency were Porges, Leimdörfer, and Marcovici[170,176] (1911,

1913) and Straub and Schlayer[208] (1912). Almost from the same time we have Sellards'[196, 197] investigations from Johns Hopkins Hospital in Baltimore (1912, 1914) as well as Palmer and Henderson[157] (1915) and Peabody's[159] publications (1915). The first carbon dioxide determinations made on blood samples from uremia patients seem to have been made by Sellards[196] (1914), who found a reduction of the bicarbonate value to 4–10 millimols.

During the past 25 years a great deal of work has been done, especially by American investigators, to clear up the causes of renal acidosis, and important results have been arrived at which, apart from Salvesen's thoroughgoing publications, do not seem to have left any deep traces in Scandinavian literature. It is in the main agreed that in this form of acidosis we are concerned with an acid retention and a total base reduction, but the quantitative significance of the individual factors in the development of the acidosis is still very uncertain. This applies especially to the surgical renal acidosis which is comparatively little investigated and still offers a rich field for research.

A general view will show that the causes of the renal acidosis are as follows:

1. Retention of phosphate (phosphoric acid).
2. Retention of sulphate (sulphuric acid).
3. Accumulation of organic acids.
4. Loss of total base (sodium and potassium) on account of:
   a. The reduced ability of the kidneys to form ammonia.
   b. The reduced ability of the kidneys to excrete a highly acid urine.
   c. The reduced ability of the kidneys to retain chloride in the presence of low chloride values in the plasma.
   d. Loss of salt on account of vomitings.
   e. Reduced intake of salt on account of anorexia and nausea.

The occurrence of an increase in the phosphate content of the serum in renal insufficiency was first demonstrated by Greenwald[56] (1916) and by Marriott and Howland[129] (1916), and the finding has later been confirmed by numerous investigators. Even though there occur some few cases of uremia without phosphate retention, the increase of phosphate is so frequent in renal insufficiency that it may be designated as

one of the surest symptoms of renal lesion. Thus in serious renal insufficiency the phosphate of the plasma may rise from the normal value of 3–6 mg p. c. (c. 2 millimols) to over 20 mg p. c.. It is beyond doubt that under such circumstances the phosphate retention contributes to the development of the acidosis by supplanting the bicarbonate, but the significance of the phosphate as a cause of acidosis has previously been somewhat exaggerated, as the phosphate increase will as a rule only explain a smaller part of the bicarbonate reduction.

The retention of the sulphate would seem to play a greater role in the development of the acidosis, since in terminal nephritis a rise has been observed in the sulphate content of the plasma from a normal value of 1 mg p.c. to 26 mg p.c., corresponding to 16 milliequivalents of acid. The increased sulphate concentration in the plasma in renal diseases was first demonstrated by Denis[34] (1921); the finding has later been specially confirmed by Loeb and Benedict[122] (1927), by Wakefield, Power and Keith[222] (1931), and by Øllgaard[236] (1937).

It has been maintained in several quarters, thus notably by Peters and co-workers,[164] Salvesen,[189] and Becher, Enger and Herrmann[15] that in renal acidosis there is often a considerable organic acidosis with accumulation of organic acids in the blood. It is as yet difficult to express an opinion on this contention which has gained the adherence of an ever-increasing number of investigators, since the determination of the organic acids in the plasma is mostly made by indirect calculation by subtracting the chloride, bicarbonate, sulphate, phosphate and protein values from the total base value (see p. 20). In a number of cases the sulphate determination is omitted; this results in indeterminable conditions since, as we have already mentioned, the sulphate content is often considerably increased in renal acidosis. It must be considered probable, however, that in inanition of long duration (in anorexia and vomiting) there is an increased keto-acid value in the blood and that, as demonstrated by Jervell, an increased lactic acid content will often occur in anoxemia and cardiac decompensation. It has been shown by the author[87] by direct analysis (1933) that there is often an excessive increase of the amino acid content of the blood in uremia. These amino acids, which are no doubt in part derived from the breaking down of the tissues, do not, however, to any appreciable

degree contribute to the development of the acidosis since with a few exceptions they do not supplant the bicarbonate. It would not be unreasonable to suppose, however, that the organic acids formed by the deaminisation of the amino acids would likewise accumulate in the blood. To decide the important question as to the presence and character of organic acidosis in uremia, the possession of a larger material, supplemented by direct analyses of various organic acids, would be necessary.

As a very important cause of the development of acidosis in renal insufficiency we may finally point out the occurrence of a total base deficit. The frequency of such a deficit appears from investigations by Peters[161] who found considerably reduced values in 97 out of 185 cases, and in 39 cases even found a reduction to below 140 milliequivalents (normal value 155 milliequivalents). As already mentioned, there are several factors which in severe renal diseases contribute to an abnormal loss of total base (sodium and potassium). In the first place the ability of the kidneys to form ammonia is much reduced, a fact first pointed out by Palmer and Henderson[157] in 1915, and later confirmed in several quarters (for instance by Van Slyke and collaborators,[220] 1926). The reduced production of ammonia which is an extremely characteristic symptom in severe renal diseases, renders it necessary for the organism to use sodium and potassium instead of ammonia for the neutralisation of the excreted acids (chloride, sulphate, phosphate). The limited ability to excrete a very acid urine will also involve a larger consumption of sodium and potassium in the excretion of the acids. As a third cause of the total base reduction we may mention the reduced power of the diseased kidney to retain chloride in the presence of low chloride values of the serum (Peters and co-workers[165] 1929). While the chloride excretion in the urine normally ceases almost entirely when the chloride content of the plasma is reduced from the normal value of 100–110 millimols to c. 95 millimols (cp. the almost discontinued excretion of chloride in several cases of pneumonia), in chronic nephritis a considerable excretion of chloride is often seen at plasma values far below this limit. Since, owing to the failing production of ammonia, sufficient ammonia is not available for neutralisation, the excretion of chloride takes place in combination with sodium and potassium. Finally, of great importance for the reduction of the

total base content of the plasma is the loss of salt in the vomitings in many cases of uremia. As these in consequence of the presence of a uremic gastritis often do not contain free hydrochloric acid (McEnery, Meyer ,and Ivy;[131] Salvesen[190]) the loss of salt in the vomitings will especially aggravate the acidosis. This loss of salt in the vomitings in connection with the reduced salt intake due to the nausea is presumably the chief cause of the total base reduction in uremia; at any rate, the lowest total base values are most frequently found in patients in whom the vomitings dominate the clinical picture.

As in the other forms of acidosis, the dehydration and acidosis often contribute much towards the development of the uremia. Following bicarbonate treatment a very considerable decrease of the blood urea values is often observed, which will frequently set in before the improvement in the renal function, a fact which must no doubt be explained by a decrease of the tissue cell destruction. In Denmark it is especially Aalkjær,[1] who has turned his attention to the increase in the blood urea due to the acidosis in renal diseases (particularly prostatic hypertrophy). The latter must, however, be supposed to be of the very same character as in the other forms of acidosis (see p. 27). Acidotic uremia in prostatic hypertrophy is, however, of very special practical interest on account of the frequent occurrence of the disease and the great therapeutic possibilities.

Even though the development of the acidosis is dependent on the renal insufficiency which is present and the acidosis therefore, as already stated, presents a fairly uniform clinical picture, reference to the therapeutic indications and possibilities in the individual renal diseases will nevertheless be necessary. Concerning the share taken by renal insufficiency in the development of acidosis in cardiac decompensation the reader is referred to p. 116.

1. Acute Nephritis. 2. Nephritis in Mercuric Chloride Poisoning.

In *acute nephritis* a considerable acidosis is hardly very frequent, but investigations on this point are still scarce. More extensive studies on acidosis in acute nephritis have especially been published by American and Norwegian

investigators (Chase and Meyer[24] 1920, Atchley and collaborators[6] 1923, Hartmann and Darrow[67] 1928, Salvesen[189] 1928). In cases of acute nephritis with eclampsia the convulsions seem to be an important factor in bringing about an accumulation of lactic acid in the blood (Salvesen); whether the lactic acid acidosis is of any great significance in the other forms of acute nephritis must so far be regarded as doubtful.

In acute glomerulonephritis the final prognosis will be fairly independent of the impaired function in the first stage of the disease; even if the urea clearance be reduced to 10 p.c. of the normal at the beginning of the disease, this is not necessarily a serious prognostic sign. An acidosis which has developed as a result of acute reduction of the renal function will therefore have a chance of being relieved simultaneously with the improvement of the kidney function on the spontaneous recovery of the disease. An instructive case of this kind (nephritis in mercuric chloride poisoning) has been reported by Rathery, Trocmé and Marie and is reproduced in the table below.

Whether it is generally advisable in acute glomerulonephritis to treat the acidosis by intravenous injection of bicarbonate solution (or by peroral ingestion of bicarbonate) cannot yet be decided, sufficient clinical data not being at hand. In view of the presence of capillary lesions in the acute stage of the disease, the administration of fluid and saline is perhaps contra-indicated. In severe acidosis with grave uremia and oliguria, however, it must presumably be allowable to try the treatment. This reserve does not apply to *nephritis in acute mercuric chloride poisoning* in which the value of the alkali therapy has been proved with certainty. It is especially the American school which has pointed out the significance of the acidosis in the intoxication syndrome and has introduced alkali treatment of this form of acidosis (Weiss[229,230]). As far back as 1917 Weiss could record 25 cases of mercuric chloride poisoning treated without deaths with intravenous injection of a 1 p.c. sodium carbonate solution; in the succeeding year the number of cases treated was 54 with only 3 deaths. In 1918 MacNider[125] induced acidosis experimentally by mercuric chloride poisoning in dogs, by which Weiss's therapy obtained the necessary theoretical support. Later on especially Rosenbloom (1919) in America has studied mercuric chloride poisoning and its treatment. In France too, the alkali therapy has been adopted

Table 7.

Residual nitrogen, plasma bicarbonate, and diuresis during the course of a recovered case of nephritis in mercuric chloride poisoning.

After Rathery, F., Trocmé and Marie, J., »Acidose dans les néphrites«, Presse méd., *35:* 921, 1927.

Day of illness	Residual nitrogen mg p. c.	Plasma bicarbonate millimols	Diuresis c. c.
1	100	19	0
5	342	14	20
8	464	11	600
13	512	12	2000
15	584	19	1300
21	248	23	2000
26	49	30	1700

with success (Binet and Marek[42]) and is generally given due recognition; it seems to be agreed that the treatment has usually a very favourable effect on the diuresis and the general condition. The value of alkali therapy in mercuric chloride nephritis has been pertinently defined by Rossier and Mercier[186] in these words: »Un jour gagné par la neutralisation d'une acidose est une chance donné de plus au rein de se regénérer, une chance de plus de guérison.«

3. Nephritis in the Eclampsia of Pregnancy.

In *the nephritis of eclampsia in pregnancy* a severe acidosis is also occasionally observed, but this form has as yet only been little investigated (Wilson[232] 1927, Stander and co-workers[204] 1939). It is possible that the acidosis, as in the cases of acute nephritis described by Salvesen, is in part due to the accumulation of lactic acid during the convulsive attacks; it must be supposed, however, that the renal insufficiency itself is usually the chief cause of the bicarbonate reduction. 2 recovered cases of eclampsia with severe acidosis treated at the Maternity Hospital, Copenhagen, are reported below. (Case records Nos. 27 and 28). The cases illustrate the point of view emphasised by the author that the acidosis in medical renal diseases need not necessarily indicate a hopeless

prognosis, and further show the effect of a treatment with isotonic sodium bicarbonate solution.

4. Chronic Nephritis. 5. Renal Amyloidosis.

In *chronic medical renal diseases* alkali treatment will often be without influence on the course of the disease; this is no doubt due to the fact that numerous other factors besides the acidosis are the cause of the serious clinical symptoms. In the author's experience, however, it is sometimes possible even in these affections to obtain considerable therapeutic results. In not a few cases of uremia in chronic nephritis the uremic condition has been released by an acute nephritis superimposed on the renal lesion already present, and causing a sudden, rapid reduction of the renal function. If it is possible to keep the patient alive during the acute aggravation, a disappearance of the uremic symptoms will not rarely be seen and a return of the renal function to its previous (reduced) level. During a stay several years long in Van Slyke's Department for Renal Diseases at the Rockefeller Hospital in New York the author has in many cases seen such a course. In the uremic period there will often be a considerable acidosis the relief of which occasionally in a spectacular way contributes to the improvement of the condition. Even though the final prognosis is serious owing to the merciless progress of the renal disease, it is nevertheless possible by means of this treatment to procure for the patient a tolerably desirable existence for several months or years. A particulary instructive case of this kind is described in Case record No. 33. In such instances in which it has been possible, before the onset of the uremia, to follow the patient's renal function, and a gradual decline in the urea clearance to values around 5—8 p.c. has been seen, no essential prolongation of the patients' lives can be expected by treating the acidosis. Whether or not one should treat it in such cases, will depend on the symptoms present and on external conditions. If the patient is still conscious but troubled by dyspnea and restlessness, it should be remembered that injection of bicarbonate is to a great extent able to relieve these symptoms, and that the treatment is even often followed by a euphoric state of mind. If the patient is already in coma, it is sometimes possible to restore con-

sciousness by this treatment, perhaps for a space of several days, if this is thought advisable for the sake of the relatives or the patient's dispositions.

The question as to the significance of the peroral ingestion of bicarbonate in the treatment of renal acidosis prior to the development of clinical uremic symptoms has not yet been subjected to a close investigation. Since, however, in certain renal diseases, particularly *renal amyloidosis*, an acidotic period of several years often precedes the final breakdown (Salvesen[190]), a moderate administration of bicarbonate in the shape of tablets or powders will presumably be of value in such circumstances for the restitution of the total base values. Conversely, in the presence of acidosis, the administration of acidotic remedies (calcium chloride, ammonium chloride) may bring about a serious aggravation of the general condition and cause the development of an acute uremic condition (see Case record No. 38). This fact is of practical significance (Johansen and Warburg;[85] Hagens[60]) as acidotic remedies are quite extensively used in the treatment of infections of the urinary ducts and edemas. It can therefore be strongly recommended to determine the bicarbonate content of the plasma before using these drugs in cases where acidosis may be supposed to be present, and not to prescribe them in the presence of renal insufficiency.

6. Prostatic Hypertrophy.

In cases of *prostatic hypertrophy* necessitating hospitalisation acidosis is a frequent finding. This appears plainly from a survey taken by Abrahamsen and Aalkjær.[175] In 39 out of 123 cases, or about 1/3, they found a reduction of the bicarbonate content of the plasma. This fact is of the greatest interest for though, as far as the author knows, there has been no after-examination with bicarbonate determination in any large group of operated prostatics, *it is allowable to infer with great certainty that the renal changes in the disease are very largely reparable, so that we have here a renal form of acidosis with a comparatively good prognosis.* Thus the finding of even severe acidosis does not exclude the recovery of the patient (see Case records Nos. 35 and 37). The as a rule good general condition which follows successful prostatectomy must in the author's opinion, even in

the absence of sufficient analytical material, indicate that the acidosis has been relieved following the improvement in the renal function caused by the drainage and the operation. Since the improvement is usually lasting this means *that in many cases there is no recurrence of the acidosis.*

Though it is possible to relieve the acidosis exclusively by catheter treatment and resection, the knowledge of the occurrence of the acidosis in prostatic hypertrophy is of the greatest significance since it is often possible to relieve it by bicarbonate treatment in the course of 24 hours and bring about a frequently spectacular improvement of the general condition. Thus relief of the nausea, want of appetite, headache, and thirst is not rarely observed following the injection of bicarbonate, while at the same time the tongue often becomes moist and the senses clear. As previously mentioned (pp. 27 and 127), the bicarbonate treatment is frequently succeeded by a considerable fall in the blood urea concentration indicating a reduction in the tissue cell destruction. The bicarbonate treatment thus renders possible a considerable curtailment of the pre-operative period and reduces the risk of the development of a uremic vicious circle (see p. 27), and of the occurrence of other complications in the prolonged exhausted condition. As a rule administration of a few litres of bicarbonate solution will be enough to bring about the desired improvement, in rarer cases, however, the injection of large bicarbonate doses will be necessary (see Case record No. 37).

7. Other Surgical Urinary Diseases.

In the other surgical diseases of the urinary system, such as *renal calculus, strictures of the urinary tract, kidney tumours, urinary infections,* the occurrence of an acidosis is likewise dependent on the degree of the functional reduction, and the prognosis of the acidosis will depend on the possibility of a restitution of the renal function. If such a possibility is present one should not hesitate to treat the acidosis, and the result of the treatment will sometimes be satisfactory (see Case record No. 38). Extensive investigations on the frequency of acidosis in infections of the urinary system are not yet available. It is beyond doubt that in these affections there is often a severe acidosis, but in the author's

experience the destruction of the renal tissue (pyonephrosis) is often so considerable that in spite of a transitory striking result of the bicarbonate treatment final recovery is not possible.

As a symptomatic treatment the intravenous bicarbonate therapy has been used with success at the »L'Institut du Cancer de la Faculté de Médecine« in Paris by Huguenin and co-workers[81] in renal insufficiency due to compression of the ureters caused by the growth of a uterine carcinoma into the parametria. The effect on the clinical symptoms is characterised as »apparement dramatique«, and it is added that ..... »la thérapeutique bicarbonatée a produit une amélioration, aussi bien du syndrome clinique que du syndrome humoral, amélioration seulement passagère par la force des choses, mais toujours évidente et souvent considérable.«

The special circumstances met with in the bicarbonate treatment of the renal acidosis with a view to the danger of tetanic symptoms following bicarbonate injection have been discussed in detail on p. 34.

The first case record shows an instance of eclampsia of pregnancy. Uremia and oliguria develop, and a moderate acidosis. During treatment with isotonic sodium bicarbonate solution (and lumbar anesthesia) a very considerable increase in the diuresis took place. The disease terminated with the recovery of the patient.

Case record No. 27. Eclampsia.

(The Maternity Hospital, Copenhagen).

A housewife, aged 26, who had had pleurisy in 1933 and pneumonia and otitis media in 1937 but had not previously showed symptoms of renal disease, was admitted on June 14, 1939, to a maternity hospital in Copenhagen where she gave birth to a living boy at 2 p.m.. The delivery was uncomplicated but the uterine contractions very violent. 4 hours after the delivery the patient fell ill and complained of a headache. 2 hours later (at 8 p.m.) a typical attack of eclampsia occurred with universal convulsions lasting 2—3 minutes. Morphine and chloral hydrate were at once given, after which the patient was transferred to the Lying-in Department of the Maternity Hospital.

Upon reception she was in profound sleep and limp, but now and then there was some grimacing. The temperature was normal,

the blood pressure 110/50. The urine contained albumen and erythrocytes, but no casts.

The condition remained unchanged until June 16 when the patient, though somewhat semi-conscious was for the first time able to answer questions. An analysis of the blood was made at this stage, and showed the presence of uremia (blood urea 115 mg p.c.), so 50 c.c. of 50 p.c. glucose solution were given intravenously.

The next day (June 17) the patient was fully awake and alert. There was slight edema of the face, and the blood urea was still high (138 mg p.c.). A urea clearance determination showed a renal function of only 1 p.c.. As the diuresis in the course of the day was only 120 c.c., 1 litre of saline was injected subcutaneously, and 50 c.c. of 50 p.c. glucose solution intravenously.

On June 18, 19, and 20 the condition was, if anything, worse. There was often grimacing, the patient was very tired, slept most of the day, but when she was awake complained of headache and blurring of the vision. There was pronounced oliguria, the diuresis in three days being only 80, 50 and 75 c.c.. At this stage the bicarbonate content of the plasma was determined and the presence of a moderate acidosis was revealed (14.7 millimols). After the analysis 1 litre of isotonic sodium bicarbonate solution was given intravenously on June 20 and 21, while lumbar anesthesia was performed at the same time to increase the diuresis.

On June 22 the patient was more conscious. The bicarbonate injection was now repeated, after which a considerable improvement in the diuresis set in with amelioration of the general condition. Thus on June 21 the diuresis was 155 c.c., on June 22, 480 c.c., and on June 23, 1380 c.c.. In spite of the increasing diuresis the blood urea value remained high for a long time (June 21, 250 mg p.c., June 24, 261 mg p.c., June 27, 272 mg p.c.), just as there was distinct hypertension, 205/110. The patient did not seem to be out of danger yet and on June 25 in the evening had an attack of universal convulsions of about 2 minutes' duration.

In the time that followed the improvement was, however, beyond doubt. The diuresis remained at over 2 litres in 24 hours (June 24, 2640 c.c., June 25, 3060 c.c., June 26, 2300 c.c.), and the patient gradually grew quite clear and alert. On June 28 she was transferred to a medical department, whence she was discharged quite well and with a normal blood urea value (20 mg p.c.) on August 3.

The next record shows the course of a serious case of eclampsia. In connection with the disease acidosis and severe uremia developed which were successfully treated with repeated injections of isotonic sodium bicarbonate solution. The patient was discharged recovered 3 months after admission.

Case record Nr. 28. Eclampsia.

(The Maternity Hospital, Copenhagen).

A housemaid, aged 37, who had not previously had children and had never shown signs of renal disease, was admitted to the Maternity Hospital on December 19, 1939.

For the last fortnight she had been troubled by blurring of the vision, but had done her work until the day of admission when she was suddenly taken ill with a bad headache, nausea and vomiting and attacks of pain in the lumbar region. Albuminuria and increased blood pressure were found (180) so the patient was admitted at once.

Upon reception at the Maternity Department the blood pressure was found to be much increased, 260/140, just as there was severe albuminuria (28 ‰). The physical examination revealed edema of the face but otherwise nothing out of the ordinary.

Treatment ad modum Stroganoff was instituted but in spite of this a typical attack of eclampsia lasting a couple of minutes occurred at 2 a.m. on December 20, 3 hours after admission, and an hour later a similar attack. In the course of the morning and afternoon there were repeated vomitings and again attacks of eclampsia at 1 p.m., 6 p.m., and 9 p.m.

On December 22 the patient gave birth to a living girl. After the delivery there was pronounced headache and blurred vision as well as considerable edemas. On December 23 the condition was exacerbated, the patient being somnolent with deep and panting respiration. Analysis of the blood showed the presence of uremia and acidosis, the blood urea value being increased to 255 mg p. c., while the bicarbonate concentration of the plasma was 14 millimols. After the analysis 1 litre of sodium bicarbonate solution was injected intravenously. As the patient was also drowsy and semiconscious the next day (December 24) 1.5 litres of sodium bicarbonate solution were again given intravenously. The diuresis which had previously been 600—1000 c. c. now rose to more than 2 litres in 24 hours, and the symptoms cleared up somewhat in the days that followed, just as the edemas and the albuminuria decreased (December 20, 40 ‰ albumen, December 21, 6 ‰, December 22, 0.3 ‰, December 25, 0.1 ‰). As late as December 27 the blood urea was, however, much increased (322 mg p. c.), hence the patient was transferred to the Medical Department B of the Rigshospital for further treatment.

Upon reception in this department a distinct urinous smell of the breath was noticed. The tongue was dry and there were slight pretibial edemas. As the blood analysis showed that the acidosis had recurred (12.8 millimols) 2 litres of isotonic sodium bicarbonate solution were given subcutaneously on December 29. In the following 24 hours the patient passed 3.7 litres of urine. The bicarbonate con-

centration of the plasma was 19.3 millimols on December 30 so on this and the following day another litre of isotonic sodium bicarbonate solution was given subcutaneously. There was no later recurrence of the acidosis (plasma bicarbonate on January 1, 1940 26.1 millimols, January 3, 26.6 millimols, January 8, 25.2 millimols). The condition continued to improve, the headache and nausea disappeared, and the appetite increased. For a time the diuresis was 4-5 litres in 24 hours, at the same time the blood urea concentration rapidly decreased (December 29, 332 mg p. c., January 2, 178 mg p. c., January 6, 92 mg p. c., January 13, 39 mg p. c.). As late as January 24 the renal function was considerably reduced (15 p. c.) though at this stage the urine was free from albumen. A few days later (January 27) a considerable increase in the function had set in (62 p. c.). On January 30 the patient was allowed out of bed. She was discharged one month later, on February 29 in good health, with normal urine and renal function (74 p. c.). On January 23 the blood pressure was 115/70, on February 22, 150/100.

The case record quoted below shows the effect of bicarbonate treatment in a case of severe uremia developing in connection with a pyogenous inflammation of the thoracic wall.

Case record No. 29. Acute nephropathia, uremic coma. Abscess of the thoracic wall.

(Own observation).

A farmer's wife, aged 55, was admitted to the Medical Department of the Holstebro District Hospital with symptoms of uremic coma on January 15, 1943. In 1937 she had undergone an operation for mammary carcinoma but had previously been well. During the hospitalisation in 1937 no sign of renal disease had been found, and analysis of the urine performed by the patient's physician in the autumn of 1942 had likewise shown normal findings. The present disease had begun 3 weeks before admission with fever (39°), great fatigue, and increasing somnolence, to which had in the last few days been added pronounced nausea, thirst, and oliguria. Treatment with sulphathiazol had had no effect on the febrile condition.

Upon admission the patient was dull and drowsy with twitchings of the arms and the face. The skin was pale with a yellowish tinge, the tongue leathery dry and coated. There was distinct uremic fetor from the mouth. The temperature had risen to 38.6° the blood pressure was normal, 140/70, and ophthalmoscopy showed natural conditions. The urine contained albumen and red blood cells, but few leucocytes.

Analysis of the blood (January 16) showed uremia (blood urea 389 mg p. c.), acidosis (14.3 millimols of serum bicarbonate) and anemia (68 p. c. of hemoglobine). After the analysis 2 litres of isotonic sodium bicarbonate solution with 2.5 g of calcium gluconate added were injected intravenously.

On the following day (January 17) the condition was aggravated, the patient being less conscious and not answering when spoken to. The respiration was rapid but not very deep, at times of the Cheyne-Stokes type. The pulse was at times almost lost and there was an increasing urinous odour of the exhaled air and persistent uremic twitchings. Analysis of the blood revealed that the condition had been aggravated, as the blood urea concentration had risen to 445 mg p. c., while at the same time the acidosis, in spite of the administration of bicarbonate, had greatly increased (6.8 millimols). 2.5 litres of isotonic bicarbonate solution with 3.8 g of calcium gluconate were therefore again given intravenously.

In the course of the night that followed an essential amelioration of the condition set in, large amounts of urine being passed involuntarily. At the same time the uremic twitchings decreased and the next morning (January 18) the patient was semi-conscious. Analysis of the blood performed at this stage showed that the acidosis had been relieved (22 millimols) and that no further appreciable rise in the blood urea value had taken place (452 mg p. c.). In view of the favourable effect of the treatment 1 litre of isotonic sodium bicarbonate solution with 2.5 g of calcium gluconate was again injected intravenously, which was followed by a fairly plentiful diuresis.

In the following week (from January 19 to 26) the patient was treated with daily intravenous injection of 1 litre of 0.9 p. c. sodium chloride solution. In this period she passed 2—3.5 litres of urine daily, and the blood urea value which as late as January 19 had been 448 mg p. c. had already on January 21 decreased to 334 mg p. c. and on January 27 to 80 mg p. c.. With the decline of the uremia the condition was gradually improved, thus on January 24 the dryness of the tongue had disappeared, and on January 28 the uremic twitchings had ceased. No recurrence of the acidosis was observed, the bicarbonate value varying between 24 and 31 millimols. The temperature, however, still remained high, 38.2°-38.5°, and on January 30 there appeared laterally in the left-sided mammary cicatrice a fluctuating abscess the size of an orange, in which incision was made on February 3 with exhaustion of very large quantities of thick brownish pus, containing staphylococci. After the draining of the pus an abscess cavity as large as a child's head was revealed, and was drained. In the course of a couple of weeks the cavity was closed and the patient was discharged well on February 26. The blood urea value was, however, still at this time slightly increased (63 mg p. c.), and the urea clearance much reduced (8

p. c.). The urine contained traces of albumen but on repeated analysis gave a negative blood reaction.

Later examinations on March 30, May 3, July 5, and October 4, 1943 showed that the condition was tolerably improved. In spite of the renal function having risen to 23 p. c. the blood urea value was still somewhat increased (66—83 mg p. c.). The patient was still tired but otherwise well and could take part in the domestic work in the home.

Case record No. 30. Chronic nephritis, uremia.

(Own observation).

A municipal employee, aged 37, who for four years had suffered from nephritis, was admitted to the Medical Department of the Holstebro District Hospital on February 24, 1941. During the last few months he had felt dyspneic after quite slight exertion though otherwise able to attend to his work. Following a cold an appreciable aggravation of the condition had occurred 10 days before admission, with pronounced fatigue and headache; during the last two days also nausea, fatigue, vomitings and nose bleeding.

Upon admission the patient was somewhat low. There was a distinct uremic fetor, the tongue was coated and dry, and the skin pale with a yellowish tinge from retained urine pigment. Upon ophthalmoscopy scattered hemorrhages in the eye grounds were found, the blood pressure was increased, 210/140, and the urine contained erythrocytes and albumen. There were electrocardiographic signs of severe myocardiac changes.

Analysis of the blood revealed an increase in the blood urea to 255 mg p.c. and the presence of a moderate acidosis (plasma bicarbonate 14.8 millimols); hence 1 litre of isotonic sodium bicarbonate solution was given intravenously.

On the following day the condition was somewhat better. The patient had not vomited, and the headache had abated. There was, however, still moderate acidosis (17.8 millimols), so another litre of sodium bicarbonate solution was given.

On February 26 and 27 the patient felt well and was out of bed most of the day. He now took an ordinary diet with a good appetite. Since the bicarbonate content of the plasma was still found to be slightly reduced, 1 litre of sodium bicarbonate solution was again injected intravenously, after which the acidosis was entirely relieved (21.6 millimols). To prevent a recurrence of the acidosis 1 teaspoonful of sodium bicarbonate was given by mouth 3 times a day during the rest of his stay. The condition hereafter remained fairly satisfactory, and the patient was discharged tolerably well on April 1. During his stay in the hospital the blood urea gradually

fell, but it was still appreciably increased at his discharge (135 mg p. c.).

At a control examination one month later the patient stated that he had been well and attended to his work. As the acidosis had in the meantime recurred (15.7 millimols) the peroral bicarbonate dose was augmented.

The case record that follows shows the effect of the bicarbonate treatment in a case of uremic coma. A very considerable improvement set in following the treatment. Unfortunately during the later course a bilateral pneumonia developed, which terminated in death.

Case record No. 31. Chronic nephritis, uremia.

(Own observation).

A barber's apprentice, aged 24, was admitted to the Medical Department of the Holstebro District Hospital in a comatose condition on December 24, 1940.

He had been well until 1935 when during a hospitalisation nephritis was shown to be present, for which reason he had several times since been hospitalised. On the whole, however, he had felt well and had been able to attend to his work until two weeks before admission when he caught a cold with running at the nose and a cough. In connection with this fatigue and somnolence developed and pronounced dyspnea upon the slightest exertion. Though he went to bed at 7 p. m. it was almost impossible for him to wake in the morning and merely the effort of dressing induced considerable dyspnea. For the last four or five days nausea, vomiting, and nose bleeding had further occurred. In the course of the 24th of December he had become increasingly dull and finally unconscious.

Upon admission the patient was almost quite unconscious with pronounced Kussmaul respiration and uremic fetor of the breath. The skin was yellowish and pale with scattered marks of scratching. The tongue was quite dry, not coated. The urine contained erythrocytes and granular casts. Analysis of the blood showed the presence of uremia (blood urea 302 mg p. c.) and acidosis (plasma bicarbonate 15.8 millimols).

1 litre of isotonic bicarbonate solution with 2 g of calcium gluconate was at once given intravenously, after which the patient became more alert. In the course of the day there were repeated anacid vomitings and once nose bleeding.

On the following day, December 25, the patient was quite clear and could speak naturally. The edge of the tongue was moist, but there was still dryness in the central part of the tongue. The

bicarbonate concentration of the plasma was 19.8 millimols, the blood urea concentration 345 mg p. c.. Again 1 litre of sodium bicarbonate solution with 2 g of calcium gluconate and 50 g of glucose was injected.

On December 26 the condition had further improved. The acidosis had been relieved (24 millimols), the whole of the tongue was moist, there was no nausea and the patient could read the papers. In the course of the evening, however, the condition was suddenly aggravated, pronounced dyspnea occurring, though not of the Kussmaul type. Examination showed that a right-sided pneumonia had developed, which in the days that followed spread to the greater part of the left lung. The patient sunk more and more though he was still conscious, when death with symptoms of pneumonia supervened on December 30.

The next case record shows an instance of renal amyloidosis with severe acidosis, observed for a period of 3 years.

Case record No. 32. Amyloid renal atrophy.

(Salvesen, H. A.,[190] *»Eine fast drei Jahre lang beobachtete schwere Acidose bei einem Fall von Amyloidschrumpfniere«, Zeitschrift f. klin. Med.,* 111: *128, 1929).*

An unmarried woman, aged 53, was admitted to the Rigshospital at Kristiania on February 2, 1925. As a child she had had frost-bite in both feet which had rendered amputation of the feet necessary. Owing to the pressure of the prostheses a severe bursitis had developed on the front of the knee joints in the course of years; the inflammation was at times purulent with formation of fistulas. In 1923 she suffered from a febrile affection with headache and pain in the lumbar region. Since then there had almost always been headache, and since the summer of 1924 further dyspeptic symptoms with abdominal pain and vomitings.

Upon admission she was very pale and tired (hemoglobine 59 p. c.) with a bilateral severe prepatellar bursitis. The urine contained large quantities of albumen (12 ‰), and the blood urea was considerably increased (160 mg p. c.). During treatment with a diet poor in nitrogen the condition improved and the patient was discharged on April 30.

After her discharge, however, the headache increased again and the patient became more dull and somnolent. As the condition continued to grow worse, she was again hospitalised on May 28. The examination still showed considerable uremia (blood urea 261 mg p. c.) and the presence of a severe acidosis (plasma bicarbonate 10.5 millimols). There was purulent secretion from the fistulas on

the front of the knees. The day after admission 50 g of sodium bicarbonate were given by mouth, after which the acidosis on the following day (June 1) was entirely relieved (27.1 millimols). At the same time the blood urea concentration decreased, the patient grew more lively, and ate with a good appetite.

In the months that followed the bicarbonate administration was repeated at intervals. Following each ingestion the bicarbonate concentration of the plasma rose, while the acidosis quickly recurred after cessation of treatment. On October 20 the treatment was definitively discontinued. In spite of this the patient remained well without headache, dyspnea, and somnolence, and was discharged from the hospital on February 1, 1926. During the succeeding two years the condition was fairly satisfactory. In this period she was repeatedly examined, and at all the examinations a considerable acidosis was found (January 1926 15.7 millimols, June 1926 14.4 millimols, June 1927 14.1 millimols). The blood urea concentration ranged from 135 to 185 mg p. c..

In January 1928 inflammatory changes developed in both hands, so on February 13 the patient was sent to the Rigshospital for the third time. During her stay numerous anacid vomitings occurred which gradually became almost incessant. Simultaneously the respiration became deep and rapid of the Kussmaul type. Finally unconsciousness and uremic coma set in and on May 25 death supervened. Shortly before, the bicarbonate concentration of the plasma was 12.8 millimols, the blood urea value 428 mg p. c.. Autopsy showed the presence of typical amyloid renal atrophy.

The case record reported below illustrates a case of severe uremia with intestinal symptoms occurring during the course of a chronic renal disease (presumably renal amyloidosis with hepatic and splenic amyloidosis). By intravenous bicarbonate treatment it was possible to relieve the uremic coma and decidedly improve the condition. The patient has since been observed for 6 years by the author. There has been steady progress in the condition, the acidosis has not recurred, and the patient is now able to attend to her home and child and take part in the same amusements as others.

Case record No. 33. Uremic coma. Renal amyloidosis. Pyuria.

(Own observation).

The patient, a housewife 30 years old, from a town in West Jutland, was admitted to the Medical Department B of the Rigshospital

on August 27, 1938. She had in the main been well until 1926 when she developed jaundice accompanied by fever. There had not since then been any recurrence of the icterus. In 1934 she underwent an operation at a hospital in Copenhagen by which a thickened gall bladder was removed. After the operation the abdomen began to increase in size and in the following year distinct enlargement of the liver was observed, particularly of its right lobe which extended towards the right iliac fossa. As the abdominal pains persisted, laparotomy was again performed in 1935, on which occasion it was established that the mass felt in the right side was an enlarged lobe of the liver. During the hospitalisation albuminuria was observed. Fluoroscopic examination of the urinary system and cystoscopy showed natural conditions, just as a concentration test showed normal specific gravity of the urine. In a later examination in 1936 the size of the liver was found unchanged; the spleen was now also slightly enlarged. There was no icterus and the plasma bilirubin concentration was normal. In the winter of 1936 the patient became pregnant, the pregnancy was complicated with anemia and pyuria. Parturition was normal, but the albuminuria persisted throughout the pregnancy and afterwards. In the years after the delivery the condition became gradually worse, the patient suffering more and more from fatigue. There was often increased temperature accompanied by chills. Icterus did not occur but there was an increasing yellowish tinge of the skin (presumably due to retention of urine pigment). During the last fortnight before admission the condition had been further exacerbated, as there now occurred nausea with repeated vomiting and increasing size of the abdomen. In the same period the temperature was constantly elevated to 38.5°—40°.

Upon admission the patient was very low, slightly dyspneic. During the examination several vomitings occurred and repeated clonic spasms of the hands. She was very tired and reluctant to answer questions, but seemed to be fully conscious. There was a faint yellowish tinge of the skin, but no jaundice. The abdomen was large and distended, the liver reached 6 cm below the right costal margin. In addition a swelling corresponding to the enlarged right lobe of the liver was felt in the right lumbar region. Analysis of the urine revealed albuminuria and pyuria (with proteus infection). Ophthalmoscopy showed natural conditions and the blood pressure was normal.

In the succeeding 24 hours the patient had several greenish vomitings. On August 29 blood urea analysis was performed showing a rise to 250 mg p. c.. At this stage she was somnolent with slow and deep respiration. As the condition seemed distinctly aggravated 2 litres of saline were injected subcutaneously without any great effect.

On August 30 the patient was semi-conscious with »grosse Ath-

mung« and urinous fetor of the breath. As analysis of the blood showed the presence of a severe acidosis (plasma bicarbonate 6.2 millimols) with a rising blood urea concentration (268 mg p. c.) 2 litres of isotonic sodium bicarbonate solution and 1 g of calcium chloride were injected intravenously. During the injection the respiration became more natural, less deep, and the sensorium clearer, and after the injection the patient declared of her own accord that she felt better. On the following day, (August 31), the respiration was normal. A few days later the clinical condition had further improved, the diuresis was increasing, the blood urea concentration decreasing (September 3, 212 mg p. c., September 7, 128 mg p. c.) and the size of the abdomen had distinctly decreased. A considerable reduction of the bicarbonate content of the plasma still persisted, however, as the acidosis recurred (September 7, 12.2 millimols, September 22, 9.9 millimols). From September 22, therefore, 10 g of sodium bicarbonate were given daily by mouth, after which the bicarbonate content quickly became normal (October 6, 25.1 millimols). As late as the 9th of September the patient had a large projectile vomiting, but after this there were no more clinical uremic attacks. The blood urea value in the period September 15 to November 4 kept between 80 and 100 mg p. c., the albumen excretion in the urine between 0.1 and 0.2 ‰. The urine contained numerous leucocytes and proteus bacteria. The hemoglobine percentage which at admission had been much reduced (50 p. c.) was normal at the discharge on November 4, 93 p. c..

After her discharge the patient felt fairly well but was very tired. There was almost always increased temperature (39.0°—39.4°) and sometimes smaller vomitings. She took 15 g of sodium bicarbonate daily and drank plenty of water. On January 25, 1939 she was again admitted for examination. The abdomen was now less distended and the blood urea concentration had further decreased (53 mg p. c.). Cystoscopic examination was performed during this stay and showed the mucous membrane of the bladder to be normal; clear urine was obtained from both ureters; the portions of urine contained albumen, some leucocytes and a moderate amount of proteus bacteria. A bromsulphalein test showed no dye retention after 30 minutes. Examination made by an ear specialist revealed the presence of a severe right-sided sinusitis; following the treatment of this affection the condition was again aggravated, simultaneously with a rise in the blood urea concentration to 92 mg p. c.. After the termination of the treatment, however, the patient again felt better and the temperature became normal. During the stay there were no signs of acidosis (bicarbonate 20.8 millimols). The urea clearance shortly after the admission was 25 p. c., at the end of March 13 p. c., and upon discharge on April 17, 29 p. c..

The patient has since been examined in October 1939, May 1941, and April 1942. At the examination in 1939 the patient stated that

Fig. 15. Photograph of a patient suffering from renal amyloidosis 2½ years after recovery from uremic coma with severe acidosis. The patient is able to work and to look after her home and child without outside help. The acidosis has not recurred. Urea clearance 36 p. c..

she had felt well and had been able to attend to her household duties with the help of a servant. Her appetite had been good and she had gained in weight. Menstruation regular. The blood pressure was found to be slightly heightened, 150/90, the blood urea concentration 75 mg p. c.. The urine contained albumen and a few red blood corpuscles. There were no retinal changes, the edge of the liver extended a couple of centimetres below the right costal margin.

At the examination in 1941 the condition had further improved. Now she no longer felt ill (see photograph Fig. 15), only now and then somewhat tired. For the last 1½ years she had managed without domestic help though besides the house she had also had to look after her little child. She stated that she led a normal life, got up at 7 a. m., went to bed at 11 p. m., went out to coffee parties and in the summer cycled to the seaside where she bathed. In the

summer vacation of 1940 she had taken part in a cycle tour covering 200 km, without the exertion being too much for her.

At the physical examination the liver was found to be of natural size. The blood pressure was 140/80, ophthalmoscopy still normal. The bicarbonate content of the plasma was 22.0 millimols, so the acidosis had not recurred. The blood urea value was 40 mg p. c.. Urea clearance in 2 periods 32 and 39 p. c.. The urine contained albumen but no formed components.

At the examination in 1942 the patient was pregnant in the second month. Since the renal function was still reduced (urea clearance 33 p. c.) and the albuminuria persisted, therapeutic abortion was advised and carried out without difficulty. The patient has since been well.

Case record No. 34. Cystic kidneys.

(Means, G. H. and Rogers, O. F.,[133] *»Observations upon a case of extreme acidosis occurring in a man with bilateral cystic kidneys«. Am. J. M. Sc.,* 153: *420, 1917).*

A negro aged 46, was admitted to the Massachusetts General Hospital, Boston, on April 17, 1916. During the last five years he had suffered from nausea and vomiting and in the same period had lost much weight, and strength. Occasionally there had been some edema of the face, hands, and feet, and a moderate polyuria. In February 1916 slight traces of albumen had been found in the urine.

Upon admission in April 1916 the patient was much emaciated. A tumour was felt corresponding to the place of the right kidney. The urine contained traces of albumen, and the renal function was much reduced, the phenolsulphonephtalein excretion being less than 5 p. c. in 2 hours. The residual nitrogen value was increased to 97 mg p. c.. The patient was discharged on May 16 in a fairly good state of health, but was again admitted on June 9 with an inflammation of the right hand. 3 days after the last admission a violent dyspnea developed with maximal respiration and all the accessory muscles working. The respiratory frequency was 50 per minute (see Fig. 2). The patient was quite conscious and said that he felt as though he had been running. Analysis of the blood showed that extreme acidosis was present, the bicarbonate content of the plasma being reduced to 5.2 millimols.

Sodium bicarbonate was now administered by rectum, 10 g every 4th hour, until 2 a. m. on June 14, after which administration of bicarbonate by stomach tube (20 g every 8th hour) was begun. On June 13 the bicarbonate content of the plasma was 8.8 millimols; there was still considerable dyspnea, but not so much as on the

day before. On June 14 the patient felt better, and analysis of the blood showed that the bicarbonate concentration had risen to 16.2 millimols. The blood urea value was 322 mg p. c.. In spite of the apparent amelioration of the condition, death supervened in the afternoon. During the whole period of treatment in which a total of 110 g of sodium bicarbonate had been given in the course of 2 days, the urine had remained acid.

The autopsy revealed typical bilateral cystic kidneys as well as small cysts in the liver.

Case record No. 35. Prostatic hypertrophy.

(Hove, A.,[78] *»Prostatectomy complicated by acidosis«. J. Urol., 28: 627, 1932).*

On March 4, 1929 Dr. Hove of Washington, D. C., was called to a lawyer, aged 73, who was suffering intensely due to acute retention of urine. A catheter was passed and 750 c. c. of urine withdrawn.

The patient had had symptoms of prostatic hypertrophy for 13 years but in spite of the physician's advice had refused to have an operation. There had not previously been acute retention.

In the course of the day the patient passed small quantities of urine but catheterisation again became necessary in the afternoon. As urination would not start, he was admitted to the Garfield Hospital in the evening.

Upon admission the residual nitrogen concentration of the blood was found to be slightly increased, the bicarbonate value was 18.2 millimols. On March 7 suprapubic cystostomy was performed. The operation was successful but 3 days later on March 10 the patient got chills followed by fever and profuse perspiration. Another bicarbonate determination was made which revealed the presence of a severe acidosis (10.4 millimols). In the days that followed the condition was serious; there was often shivering, the pulse was intermittent and fast, respiration rapid and at times irregular. The patient was nervous, fractious and irritable. On March 19 the temperature was again normal but the condition was still unsatisfactory, and analysis of the blood showed that the acidosis had further increased (plasma bicarbonate 4.4 millimols).

In the succeeding days large doses of sodium bicarbonate were given partly intravenously partly by mouth. Simultaneously such a considerable improvement of the general condition was seen that on April 2 it was thought safe to perform prostatectomy, which was carried out without complications. Upon analysis of the blood on April 4 the bicarbonate value was found to be normal (21.7 millimols). On April 7 the patient could void the urine, and a week

later was able be out of bed. He was discharged to his home on April 29.

After this the condition was satisfactory, and after some time the patient could resume his practice. It must be supposed therefore that there was no recurrence of the acidosis. About 1 year later cerebral hemorrhage occurred, death supervening on May 21, 1930.

The following case record shows the pre-operative bicarbonate treatment in a case of prostatic hypertrophy with a moderate acidosis.

Case record No. 36. Prostatic hypertrophy.

(Retlev-Abrahamsen, A., and Aalkjær, V.,[175] *Brit. J. Urol., 10: 231, 1938).*

A man, aged 75, was admitted to Department D of the Bispebjerg Hospital, Copenhagen, on January 7, 1937, suffering from prostatic hypertrophy. For the last year he had had difficulty in passing the urine, but there had been no acute retention. For some time before admission he had been troubled by dryness of the throat, thirst, and dyspnea upon exertion.

Upon admission the patient was found to be uremic (blood urea concentration 165 mg p. c.) and in a bad state of nourishment. There was distinct anemia (hemoglobin 59 p. c.) and clinical signs of dehydration. The urea clearance was reduced to 18 p. c. and there was moderate acidosis (16.6 millimols). The residual urine was 1.5 litres.

A catheter was inserted and continuous urinary drainage started; in addition for 4 days in succession (Jan. 8—Jan. 11) 1 litre of 1.3 p. c. sodium bicarbonate solution was given intravenously every day. On January 12th the acidosis had been relieved (26 millimols), and the blood urea value had fallen to 138 mg p. c. while the clearance was unchanged, 18 p. c.. On January 18, 12 days after admission, transurethral resection of the prostate was performed. At this stage the blood urea concentration was 216 mg p. c., clearance 19 p. c.. The postoperative course was uneventful and the patient was discharged on January 29 *without any recurrence of the acidosis* (blood urea 102 mg p. c.). Two months later the resection had to be repeated. At a control examination on January 1938 the patient was in excellent health without residual urine.

The next record illustrates the treatment of a case of prostatic hypertrophy associated with severe acidosis, which recurred after resection of the prostate and again following an ascending infection of the urinary system. By the admini-

stration of isotonic sodium bicarbonate solution it was possible to relieve the acidosis and improve the condition. A total of 12 litres of sodium bicarbonate solution was given.

Case record No. 37. Prostatic hypertrophy.

(Retlev-Abrahamsen, A. and Aalkjær, V., [175] *Brit. J. Urol., 10: 231, 1938).*

A man, aged 63, was admitted to Department D, Bispebjerg Hospital, Copenhagen, on September 20, 1937, suffering from prostatic hypertrophy. For 20 years he had had difficulty in passing the water and during the last year before admission had been much troubled by thirst and frequent urination. There had never been acute retention.

Upon admission distinct uremia (blood urea 140 mg p. c.), much reduced function of the kidneys (clearance 15 p. c.), and pronounced acidosis (plasma bicarbonate 8.4 millimols) were observed. The residual urine was 2 litres.

Urinary drainage through a catheter was at once started, and on three days in succession (September 21—September 23) 1 litre of isotonic sodium bicarbonate solution was given intravenously. On September 24 the acidosis had been relieved (29.8 millimols) and the blood urea value had fallen to 70 mg p. c., the general condition being at the same time appreciably improved.

On October 1 transurethral prostate resection was performed, after which 1 litre of physiological sodium chloride solution was injected subcutaneously every day. In the days that followed some bleeding was observed from the site of the operation. On October 3 the patient vomited and complained of nausea, want of appetite, and headache. Analysis of the blood showed that a slight acidosis had again developed (19.4 millimols) with a rise of the blood urea value to 97 mg p. c. In the following days, therefore, a daily dose of 1 litre of sodium bicarbonate solution was given intravenously. On October 7 the acidosis had been relieved (26.2 millimols) and the nausea and headache had disappeared, while the general condition was so satisfactory that the patient was allowed to get up.

8 days later, on October 15, the patient showed signs of an ascending urinary infection. Examination of the blood showed that an acidosis had again developed (16.4 millimols) for which reason treatment with sodium bicarbonate was again instituted, 1 litre intravenously every day for 5 days. On October 21 the temperature was falling and the acidosis again relieved (26.8 millimols). The blood urea concentration had at this stage fallen to 72 mg p. c. On the following day the patient could again be out of bed and was discharged a month later.

Case record No. 38. Chronic pyelonephritis.

(Own observation).

A self-supporting lady, aged 42, was admitted to the Surgical Department C of the Rigshospital, Copenhagen, on February 10, 1939 for a urinary infection.

The illness had begun in October 1938 with nausea, vomiting and pain in both renal regions. For three weeks there was irregular temperature (37.0°—39.6°), burning upon urination and turbidity of the urine; hence she was treated by her physician with calcium chloride, prontosile, and mandelic acid, and repeated bladder irrigations.

Since the beginning of the illness the condition had been somewhat variable; in the last few months before admission the patient had sometimes been out of bed, but at other times had been obliged to keep her bed. In the period 2—8 February (i. e. just before admission) she had been treated with calcium mandelate, 10 g 4 times a day, and under this treatment had grown distinctly worse, feeling wretchedly ill with pronounced fatigue and now and then vomiting. At this stage she had besides for the first time felt dyspnea on slight exertion.

Upon admission the patient was somewhat low, pale and thin. There was tenderness of the left renal region, and analysis of the urine showed albuminuria, pyuria, and coliuria. On February 11 the blood urea concentration was determined and revealed the presence of uremia (122 mg p. c.). The urea clearance was 10 p. c., the blood pressure 155/100, ophthalmoscopy normal. There was no fever.

In the days that followed the condition was unchanged. On February 13 the blood urea concentration had mounted to 138 mg p. c.. At this stage a determination was made of the plasma bicarbonate and showed a reduction of the bicarbonate value to 16.5 millimols. On February 14, therefore, 2 litres of isotonic sodium bicarbonate solution were given intravenously after which the acidosis was relieved (26.4 millimols). The next few days a considerable improvement of the condition was observed, the patient was less tired, felt stronger, and had a good appetite. At the same time a reduction of the uremia was seen, the blood urea value on February 16 being 83 mg p. c. and on February 24, 79 mg p. c.. Cystoscopy revealed diffuse cystitis and excretion of turbid urine from the left kidney; direct pyelography showed a normal renal pelvis on both sides. During an observation period of several weeks' duration no recurrence of the acidosis took place, the plasma bicarbonate concentration being on February 21, 23.4 millimols, on February 24, 21.9 millimols, on February 27, 20.9 millimols, on March 7, 22.8 millimols, and on March 17, 20.8 millimols.

In the following months the improvement steadily progressed though the blood urea was constantly increased to more than 70 mg p. c.. On June 4 the patient was allowed to get up and on June 14 she was discharged in good health. The urine at the discharge contained some few coli bacilli and a number of leucocytes.

A gain in weight of 10 kg indicated the considerable improvement of the general condition.

Case record No. 39. Pyonephrosis. Cancer uteri. Fistula vesicovaginalis.

(Own observation).

A sempstress, aged 67, was admitted to the Medical Department of the Holstebro District Hospital on October 24, 1940 in an extremely low condition.

For a number of years she had had recurring urinary infections, and during the last year increasing incontinence. Six weeks before admission she had for a time had high fever and been obliged to keep her bed. At the same time nausea, anorexia, and pronounced fatigue set in. On October 22 she felt distinctly worse and the day before admission became semi-conscious. There was a constant discharge of bloody urine.

Upon admission to the hospital the patient was distinctly semi-conscious with typical Kussmaul respiration and urinous fetor of the breath. The skin was pale and yellowish and could be lifted up in folds which remained. The tongue was quite dry. In the left side of the abdomen at the site of the kidney was felt a cocoanut-sized mass which seemed very tender. Upon catheterisation the bladder was found quite empty. Recto-vaginal exploration showed the presence of a tumour in the lower part of the pelvis, presumably issuing from the uterus. From the vaginal opening bloody, purulent, stinking urine was evacuated, so that a vesico-vaginal fistula must be supposed to be present.

Shortly after admission a plasma bicarbonate determination was made which revealed the presence of acidosis (10.7 millimols) and uremia (blood urea concentration 200 mg p. c.). Immediately after the analysis 3 litres of isotonic sodium bicarbonate solution with 3 g of calcium gluconate were injected intravenously at one sitting. During the injection an appreciable improvement took place, the patient becoming conscious and able to answer questions. At the same time the expression of the face became more natural, the features less sunken, the tongue became moist, and there was slight perspiration. After the treatment it was no longer possible to lift up the skin in folds which remained.

Though calcium gluconate had been added to the bicarbonate

solution, slight tetanic symptoms occurred during the injection with rigidity of the fingers and an approach to laryngeal spasm.

4 hours after the bicarbonate injection a bicarbonate determination was again made which showed that the acidosis had been relieved (plasma bicarbonate 24.4 millimols). At the same time the blood urea value had decreased from 200 to 165 mg p. c..

The observed amelioration of the condition was, however, only of short duration. The patient again became unconscious and died the following morning.

G. Acidosis due to an abnormal intake of acid

1. *Sulphuric and hydrochloric acid poisoning.* 2. *Medicinal acidosis.*

1. Sulphuric and Hydrochloric Acid Poisoning.

Though acidosis was first produced experimentally by the injection of acid solutions (Walter[224]), and it was shown already in the first publications that the acidotic symptoms could be relieved by injection of sodium carbonate solution, the literature only contains a single report on the treatment of acid poisoning in man by intravenous injection of alkali. The treatment of the cauterisations produced by the acid consumed, and the neutralisation of the stomach contents, seem entirely to have dominated the therapy of these serious cases. As far as the author knows, investigations on the bicarbonate content of the blood in these intoxications are not available, apart from a single observation by Lipetz[119] of Minsk, who in a fatal case of hydrochloric acid poisoning found a reduction of the bicarbonate concentration of the plasma to 8,2 millimols.

It must be assumed that at the intake of concentrated sulphuric or hydrochloric acid solutions the absorbed amount of acid is often rather small since, owing to the local effect, only comparatively small amounts of acid reach the stomach. It is possible that, besides the shock, the extensive destruction of the cells with autolysis of the tissue contributes to the development of the acidosis (Etienne-Martin[42]). In view of the very favourable experience gained from animal experiments with the treatment of acid poisoning by bicarbonate injections it would seem advisable to keep this therapy in mind.

Below is reported the only case of a strong inorganic acid poisoning treated with injection of alkali which the author has been able to find in the literature.

Case record No. 40. Sulphuric acid poisoning.

(Marchand, F.,[127] *München. med. Wchnschr., 59: 178, 1912).*

A 24 year old farm hand had on October 19, 1911 drunk a not definitely known amount of concentrated sulphuric acid out of a bottle. Immediately after drinking it he had brought up some of the acid and had at once after this been sent to the Medical Clinic at Heidelberg. During his conveyance to the hospital he lost consciousness. Upon admission at 2.30 p. m. he was comatose with cyanosis of the face and responded neither to questions nor to pinching of the skin. There was pronounced motor unrest, the patient tossed and turned, doubled up, and uttered inarticulate sounds. There was cauterisation of the lips and cheeks and excretion of bloody saliva from the mouth. The abdomen was much distended.

Magnesium oxide was at once introduced through a soft stomach tube, while for fear of perforation the stomach was not washed out. The patient gradually grew quieter but was still quite unconscious. As the cyanosis increased and periods with dyspnea set in, tracheotomy was performed at 4 p. m.. After this the breathing was less laboured, but the cyanosis and unconsciousness persisted. As the condition did not improve, 300 c. c. of 5 p. c. sodium bicarbonate solution were injected intravenously in the evening. *Immediately after the injection the patient woke up* and asked for something to drink. There was no later recurrence of unconsciousness.

The further course was complicated by broncho-pneumonia and thrombosis of v. basilica at the site of injection. Further the cauterisation of the mouth cavity caused much distress. The final result was excellent, the patient being free from symptoms at his discharge from the hospital.

2. Medicinal Acidosis (through Administration of Calcium Chloride and Ammonium Chloride).

By giving calcium chloride or ammonium chloride in daily doses of 10 to 20 g it is possible to induce an acidosis in man, with reduction of the bicarbonate concentration to about half the normal values, the intake of these salts having the same effect as an equivalent amount of hydrochloric acid. This is due to the fact that the ammonia of the ammonium chloride

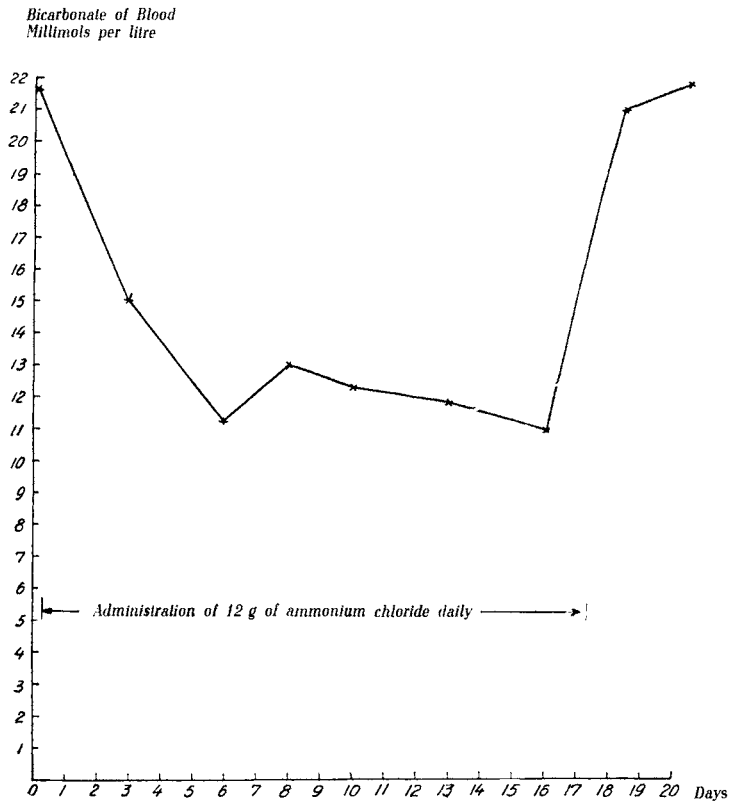

Fig. 16. Experimental acidosis.
The bicarbonate content of the blood during daily administration of 12 g of ammonium chloride to a male, aged 30. During the first 6 days of the experimental period the bicarbonate concentration fell from 21.6 to 11.3 millimols. After cessation of administration the bicarbonate value quickly rose to normal. After Koehler, A. E., »The effect of acid and base ingestion upon the acid-base balance«, J. Biol. Chem. 72: 99, 1927.

shortly after entering the liver from the intestine is transformed into urea, whereas the chloride ion remains unchanged. Of the calcium chloride the bulk of the calcium is retained in the intestine as insoluble phosphate or carbonate compounds, while the chloride is absorbed.

As an example of the experimental production of acidosis by administration of ammonium chloride I may mention the investigations made by Koehler[105] who, in an experimental

period lasting 17 days, gave 12 g of ammonium chloride daily to a male, aged 30. In the course of the first six days the bicarbonate content of the blood fell to 11.3 millimols (see Fig. 16); after the administration of ammonium chloride had been discontinued the values quickly rose to normal again. During the experiment an increase in the pulmonary ventilation from 7.8 to 15 litres per minute was observed, just as it was noticed that on quite slight exertion there was dyspnea.

The experimental inducement of acidosis by means which, like calcium chloride and ammonium chloride, have no great locally irritating effect on the gastro-intestinal tract, has been of great importance for the elucidation of the symptomatology of acidosis, as the symptoms under these circumstances are not obscured by the primary disease. Thus the description given in Chapter I of the symptoms of acidosis is in part based on observations from acidosis produced experimentally.

As is well known, the inducement of acidosis by the administration of calcium chloride and ammonium chloride has been much used in the treatment of pyuria and edemas. But, as already mentioned, in the presence of a chronic affection of the kidneys it is attended with considerable risk (Johansen and Warburg[85], Linder[118], Hagens[60]), since where acidosis is already present such a substantial reduction of the bicarbonate value may take place that an acute uremic condition sets in.

H. Acidosis in Various Other Intoxications.

1. *Salicylic acid poisoning.* 2. *Methyl salicylate poisoning.* 3. *Aspirine poisoning.* 4. *Methyl alcohol poisoning.* 5. *Methyl chloride poisoning.*

In the present chapter we shall discuss some intoxications in which the acidosis takes a prominent place in the clinical picture: salicylic acid, methyl salicylate, aspirine, methyl alcohol and methyl chloride poisoning. In certain other intoxications, too, it must be supposed that there is frequently acidosis (thus in acute arsenic poisoning with choleriform diarrheas, and in acute phosphorus poisoning), but these intoxications do not seem to have been the subject of in-

vestigation. Acute mercurial poisoning is mentioned on p. 128, fungal poisoning on p. 65 and experimental guanidine intoxication on p. 119.

1. Salicylic Acid Poisoning. 2. Methyl Salicylate Poisoning. 3. Aspirine Poisoning.

With the *salicylic acid* doses used in therapy acidotic poisoning is rare, but the intoxication which especially occurs in children is very characteristic. The most striking symptoms are dyspnea of the Kussmaul type (the so-called »salicylic dyspnea«, first described by Quincke in 1882) and somnolence. In addition there is often, but not always, a reduction of the bicarbonate content of the plasma, which in some instances may be very considerable (see Case record No. 41). Since the intoxication may occur after the intake of very small doses of salicylic acid (thus poisoning has been seen after the consumption of 1 g of salicylic acid), it must be supposed that the acidosis is not in the first place due to the salicylic acid supplanting the bicarbonate, while the dyspnea is presumably often due to a specific effect of the salicylic acid on the respiratory centre; indeed, the available investigations would seem to show that the acidosis is principally the result of an accumulation of keto-acids in the blood. An excellent survey of the salicylic acid acidosis with numerous case reports is found in a thesis for the doctorate by Nathalie Roche[176] (1937), entitled »Les accidents d'acidose au cours du traitement salicylé«. In Scandinavia the subject has been treated by Odin[153] in 1932. A review of the clinical aspect of *methylsalicylate* poisoning and the occurrence of acidosis in this intoxication has recently been published by Shireff and Pearlman[199].

In *aspirine* poisoning, which is very frequent in Hungary where more than 100 attempts at suicide by acetylsalicylic acid are reported annually, a reduction of the bicarbonate content of the plasma to less than 15 millimols (Balázs[10]) has been observed after the intake of single doses of 20—30 g. As it is most frequently a single large dose of the drug that has been taken, it is possible that there is here a direct acidotic action of the acetylsalicylic acid (with supplanting of the bicarbonate by the acid).

As a treatment of salicylic acid and aspirine poisoning,

intravenous injection of sodium bicarbonate (Merle[42]) has often been used with success. In view of the fact that severe ketonemia is very often a feature of salicylic acid poisoning, treatment with glucose must also be regarded as indicated (Roche[176]).

Case record No. 41. Salicylic acid poisoning with acidosis.

(Paisseau, G., Friedmann, E., and Vaille, C.[156] *»Intoxication mortelle par le salicylate de soude«, Bull. et mém. Soc. méd. d. hôp. de Paris,* 50: *1211, 1934).*

A girl, 10 years old, was admitted to L'Hôpital Trousseau in Paris on December 6, 1935. 4 months earlier she had had an acute attack of polyarthroitis; immediately before the admission a recurrence of the affection of the joints had taken place. Upon admission the child was subfebrile (38°); the examination revealed a systolic murmur at the apex of the heart, but otherwise nothing out of the ordinary.

Treatment with 10 g of salicylic acid and 20 g of sodium bicarbonate daily was at once instituted. Since, however, some few vomitings occurred on the 8th of December the salicylic acid was subsequently injected intravenously (2 g daily) and rectally (5 g daily in combination with 10 g of sodium bicarbonate). The following days the condition was satisfactory, but on December 10 the child seemed somewhat low and on December 11 she was somnolent with repeated vomitings, hence the salicylic acid was discontinued.

In the course of December 11 dyspnea of the Kussmaul type occurred. Examination of the urine disclosed large amounts of keton bodies: acetone, acetoacetic acid, and β-hydroxybutyric acid. Analysis of the blood showed the presence of a severe acidosis (3.9 millimols) as well as an increase of the blood urea to 128 mg p. c..

Sodium bicarbonate solution was now given intravenously, subcutaneously, rectally, and by mouth, 54 g of sodium bicarbonate in all, and in addition 10 units of insulin subcutaneously, after which a considerable improvement took place which persisted till the following morning (December 12). Analysis of the blood showed a rise in the bicarbonate content to 14.0 millimols, while the blood urea concentration had fallen to 99 mg p. c.. On December 13 the condition seemed satisfactory, but at this stage albuminuria and the presence af granular casts in the urine was first observed. Hence 250 c. c. of sodium bicarbonate solution were again given subcutaneously, as well as 10 units of insulin. In spite of apparent improvement the child suddenly became comatose at 9 p. m. and died shortly after.

Case record No. 42. Salicylic acid poisoning with acidosis.

(Labbé, M., Boulin, R. Uhry and Ullmann,[110] *»Coma acidosique et traitement salicylé.« Bull. et mém. Soc. méd. d. hôp. de Paris,* 51: *1321, 1935).*

A woman, aged 25, was admitted to L'Hôpital Cochin in Paris on May 15, 1934 in a comatose condition. In the two preceding weeks she had daily taken 12 g of salicylic acid by mouth for a rheumatic polyarthroitis. Apart from nausea and ringing in the ears there had been no special symptoms, but on May 15, after a short period of delirium, a comatose condition suddenly set in.

Upon admission there was pronounced coma with dyspnea of the Kussmaul type. The examination revealed nothing special beyond considerable albuminuria and the presence of a severe acidosis (plasma bicarbonate 7.9 millimols). The urine contained traces of keton bodies.

50 g of sodium bicarbonate were at once given (parenterally and rectally) with the result that on the following day (May 16) the bicarbonate concentration of the plasma had mounted to 18.5 millimols. As the dyspnea persisted and the temperature had risen much (41.7°) 100 g of sodium bicarbonate were further given.

On May 17 the patient roused from her coma, and the dyspnea disappeared. Analysis of the blood showed that the acidosis had been relieved (29.5 millimols). At this stage the urine no longer contained albumen. The following days the improvement coutinued, and the patient was discharged from the hospital on May 24.

Case record No. 43. Methyl salicylate poisoning.

(Pincus, J. P. and Handley, H. E.,[168] *»Report of a Case of Fatal Methyl Salicylate Poisoning«, Bull. Johns Hopkins Hosp.,* 41: *163, 1927).*

A child, 22 months old, was admitted to the Johns Hopkins Hospital at Baltimore on April 7, 1927. 10 hours before admission the child had drunk an unknown quantity of winter green oil. 5 minutes after the intake there had been vomiting. Scarcely an hour later the mother took the child to a drug store, whose owner prescribed 2 c. c. of Extractum fluidum ipecacuanhæ and reassured the mother as to the danger of the case. In the following hours there were several vomitings which smelt of winter green oil. In the course of the evening the mother noticed that the child's limbs were growing colder, so it was quickly taken to the hospital.

Upon admission the child was able to sit up and stand alone. There was distinct dyspnea with deep inspirations and expirations.

Otherwise the examination showed nothing out of the ordinary and the child did not seem critically ill.

About an hour after admission clonic convulsions occurred which continued intermittently for the following two hours. Analysis of the blood at this stage showed the presence of a moderate acidosis and the child died 4 hours after admission.

Case record No. 44. Aspirine poisoning.

(Own observation).

A waitress, aged 21, on September 10, 1941, intending to commit suicide took about 30 tablets of phenacetyl c. codein (with an acetylsalicylic acid content of about 8 g). On the same evening at 9 p. m. she was admitted to the Medical Department of the District Hospital at Holstebro.

Upon admission the patient was not very ill, but it was observed that there was distinct dyspnea with a respiratory rate of 32. There was further moderate cyanosis of the lips and finger-tips (presumably due to the intake of phenacetin), but otherwise the examination showed nothing special.

The stomach was at once washed out until the water no longer reacted to ferrichloride. After this a blood sample was taken for bicarbonate analysis; it showed a plasma concentration of 21.7 millimols. In view of the presumed methemoglobinemia 25 c. c. of Sol. methylthionini chloridi were injected intravenously (corresponding to a methylene blue dose of 25 cg). In addition 1 litre of physiological sodium chloride solution was given subcutaneously.

The patient spent a restless night, but was tolerably well the next day (September 11). The cyanosis had disappeared but there was still distinct dyspnea. Analysis of the blood showed that a moderate acidosis had developed (plasma bicarbonate 18.5 millimols). The urine reacted strongly to acetoacetic acid and acetone, but a determination of the total content of acetone in the blood (according to the method of Van Slyke and Fitz) showed no ketonemia worth mentioning (5.9 mg p. c., corresponding to 1.0 millimols). In view of the presence of acidosis and ketonuria 1 litre of isotonic sodium bicarbonate solution with 50 g of glucose and 20 international units of insulin was injected intravenously.

On September 12 there was a further improvement in the condition. The acidosis had been relieved (plasma bicarbonate 21.5 millimols) and the rate of respiration was 20. As late as September 13 an appreciable ketonuria was observed. There was no recurrence of the acidosis (plasma bicarbonate 22.7 millimols).

On September 15 the urine was for the first time free from salicylic acid. On the same day the patient was discharged quite well.

4. Methyl Alcohol Poisoning. 5. Methyl Chloride Poisoning.

In *methyl alcohol poisoning,* which is of special practical interest on account of its frequency, there seems to be a special form of acidosis, a *formic acid acidosis.* As early as 1893 as it was shown by Pohl[169] that methyl alcohol is converted into formic acid in the organism. The presence of acidosis was demonstrated in 1920 by Harrop and Benedict[64] who in a case of methyl alcohol poisoning found the bicarbonate content of the plasma reduced to 15.8 millimols (see Case record No. 45). In a case observed by Rabinowitch[173] a few years later the bicarbonate concentration had been reduced to 11.3 millimols. In 1931 Ustvedt[213] published 3 cases of methyl alcohol poisoning treated at the Ullevaal Hospital in Oslo. In all the patients there was marked Kussmaul respiration and considerable acidosis (the bicarbonate concentration of the plasma was 7.8, 9.5, and 8.3 millimols). In one of the cases there was a difference of 30 millimols between the total base value and the directly determinable acid components, which indicated the presence of large amounts of organic acids. Thorough chemical investigations on poisoning in man are not yet available, but it is probable that it is the formic acid produced by the oxidation of the methyl alcohol which is the cause of the acidosis and is responsible for at any rate some of the symptoms of poisoning.

In the United States, during the prohibition period, the intravenous injection of a 5 p. c. sodium bicarbonate solution was largely used as a treatment for this intoxication, a therapy which was first introduced by Harrop and Benedict. In many cases the injection seems to have a decidedly favourable influence on the course of the disease, notably there will often be a considerable relief of the distressing dyspnea (Lambert[148]).

Case record No. 45. Methyl alcohol poisoning.

(Harrop, A. and Benedict, E. M.,[64] *»Acute methyl alcohol poisoning associated with acidosis. Report of a case«. J.A.M.A. 74: 25, 1920).*

An actress at Baltimore, aged 25, on November 22, 1918 drank about 250 c. c. of alcohol stated to be brandy but which on a later analysis proved to contain 87 p. c. of methyl alcohol. On the after-

noon of the following day she felt ill with nausea. On the morning of November 24 she vomited once or twice and at the same time noticed great impairment of sight. Further there was headache, pronounced thirst and considerable dyspnea. On the same evening she was admitted to Johns Hopkins Hospital.

Upon admission the patient was semi-conscious and cyanotic with deep and rapid respiration; at this stage she was unable to see. In the following hours the dyspnea was aggravated.

A determination of the bicarbonate content of the plasma at midnight revealed the presence of a moderate acidosis (15.8 millimols). After the analysis 400 c. c. of 5 p. c. sodium bicarbonate solution were injected intravenously. On the next day, November 25, the dyspnea was less marked. As the bicarbonate value was still considerably reduced (15.7 millimols) the treatment was repeated with injection of 500 c. c. of 5 p. c. sodium bicarbonate solution, after which the acidosis did not recur. Apart from a short period with hallucinations the further course was uncomplicated. The sight gradually returned and the patient was discharged on December 23.

Case record No. 46. Methyl alcohol poisoning.

(Ustvedt, H. J. and Mohn, A.,[214] *»Tresprittforgiftning og acidose« (Methyl Alcohol Poisoning and Acidosis). Norsk mag. f. Lægevidensk., 93: 1191, 1932).*

A man, aged 30, was admitted to the Ullevaal Hospital, Oslo, on October 27, 1931 in the evening with the diagnosis of uremia. He had been taken ill the same morning with a headache, abdominal pains, and vomiting. Upon admission the patient was soporose and could not give exact information. It later transpired that on October 25 he had drunk alcohol of doubtful origin. There was marked »grosse Athmung« with a respiration rate of 26, the exhaled air had a peculiar smell which, however, did not resemble that of acetone. The tongue was dry, and there was constant vomiting. The patient complained of impaired sight; examination of the eyes showed the presence of a sense of light but he was unable to count fingers. Opthalmoscopy and other physical examinations disclosed nothing out of the ordinary. Analysis of the blood revealed that the bicarbonate content of the plasma was reduced to 7.8 millimols, so that there was severe acidosis. The blood sugar value was 122 mg p. c., blood urea concentration 70 mg p. c.. The urine contained albumen, erythrocytes, and casts.

3 hours after admission the patient was nearly comatose. Therefore 500 c. c. of 5 p. c. glucose solution were given intravenously, as well as 1 litre of 3 p. c. glucose rectally, and 40 units of insulin subcutaneously.

On the following day (October 28) the patient was somewhat

more lucid but still very drowsy. There were repeated vomitings which upon analysis were found to contain methyl alcohol. Analysis of the blood showed a distinct rise in the bicarbonate content, the plasma concentration being 13.0 millimols. In the course of the day the »grosse Athmung« disappeared. The patient continued to show signs of improvement and was later discharged well.

In acute poisoning with *methyl chloride,* a gas extensively used in refrigerating plants, a clinical picture often occurs which bears a great resemblance to methyl alcohol poisoning. Even though few reports of bicarbonate analyses in this form of poisoning are as yet available, it seems beyond doubt that in severe cases of intoxication an acidosis may occur, the nature of which, however, is not yet established. As formic acid has often been found in the urine of the poisoned patients, this acid is perhaps, as in methyl alcohol poisoning, of significance for the causation of the acidosis. In 1942 Scherwin[191] surveyed the acute methyl chloride poisoning and described 2 cases.

Case record No. 47. Methyl chloride poisoning.

(Scherwin, J.,[191] *2 Tilfælde af acut Methylchloridforgiftning ledsaget af Acidose. (2 Cases of Methyl Chloride Poisoning accompanied by Acidosis). Ugesk. f. Læger,* 104: *1421, 1942).*

A business manageress, aged 35, was admitted to the Marselisborg Hospital in Aarhus on December 8, 1941, in a very low condition. She had been taken ill 1 week before admission with vomitings, diarrhea, and abdominal pains, as well as increasing semiconsciousness and hallucinations. At the admission it was stated that in her flat a valve had burst in the refrigerating plant which was worked by methyl chloride, so that for several days she had presumably been exposed to the action of considerable amounts of methyl chloride.

When admitted to the hospital the patient was precomatose and responded only faintly when addressed; there was slight cyanosis and a distinct aromatic odour of the air exhaled, the urine contained keton bodies, and analysis of the blood showed a moderate acidosis (16.8 millimols) and a sligthly elevated blood urea value (74 mg p. c.).

In view of the presence of acidosis 1.4 litres of isotonic sodium bicarbonate solution and 1 litre of glucose saline were given intravenously. During the injection the patient became more alert and was

able to answer questions, just as the appearance improved considerably. Already the next day the acidosis had been relieved (28.0 millimols) and the blood urea value was normal (40 mg p. c.). The patient was still for several days semi-conscious and confused and until her discharge on January 21, 1942 complained of fatigue, lassitude, and nervousness. At the after-examination a month later her condition had, however, improved considerably.

J. Other Forms of Acidosis not yet fully elucidated.

1. Liver insufficiency. 2. Acute febrile affections of the bile ducts and the liver. 3. Acidosis in thyreotoxicosis. 4. Acidosis in acute suppurative otitis media in infants. 5. Acidosis in other serious infections and septic conditions.

In the preceding sections we have described in more detail the circumstances causing the development of acidosis in the individual groups of diseases. From our exposition it will appear that the causation must in the main be regarded as cleared up.

But under certain other circumstances acidosis will also develop without it being possible to point out the cause with certainty, because close investigations are not yet available. The most important of these forms of acidosis which will be discussed in the present chapter are the acidosis in liver insufficiency, in serious febrile affections of the bile ducts and liver, in thyreotoxicosis, in severe cases of acute otitis media in infants, and in other serious infections and septic conditions.

1. Acidosis in Liver Insufficiency.

The presence of acidosis in liver insufficiency has been described by several authors. Thus Schmitt and Basse[193] found considerable acidosis (9.8, 14.1, and 11.6 millimols) in three fatal cases of liver disease, and Csapó[31] found reduction of the bicarbonate content to 6.2 millimols in a case of acute

yellow atrophy of the liver in a child 18 months old. Nonnenbruch[151] too states that he has found acidosis in hepatic coma. Acidosis does not seem to occur regularly in liver insufficiency, however, thus the bicarbonate concentration was not reduced in a case of acute yellow atrophy of the liver examined by Stadie and Van Slyke[203].

As the cause of the acidosis several investigators have pointed out a rise in the lactic acid content of the blood, but thorough researches on this form of acidosis are still lacking. It is quite probable that the mechanism in certain cases of hepatic coma is the same as in the development of premortal acidosis. In other instances a reduction of the renal function due to the hepatic affection may be a concurrent cause (»hepato-renal syndrome«, see p. 164). As systematic investigations are lacking the description in this work will be limited to a report of the cases.

Case record No. 48.
Hepatic cirrhosis with liver insufficiency.

(Allen, F. M.[3] »Observations in the terminal stage of a case of hepatic cirrhosis«. Am. J. M. Sc., 158: 307, 1919).

A soldier, aged 29, who had had syphilis in 1912, was admitted to the Military Hospital in Lakewood, New Jersey, in February 1919. 6 months previously there had been accumulation of fluid in the abdomen which had rendered necessary several paracentheses. The evacuated ascites fluid showed a positive Wassermann reaction.

During the stay in the hospital the ascites recurred, but the condition remained in the main unchanged until March 7 when the patient unexpectedly became comatose. On the following morning the coma was unchanged and at this stage there was pronounced dyspnea with stertorous, deep, and rapid respiration. Analysis of the blood showed the presence of a moderate acidosis (16.3 millimols). As the condition became aggravated, 3 litres of physiological saline solution with 10 p. c. glucose were injected intraperitoneally in the morning, and 500 c. c. of 5 p. c. glucose solution intravenously at 2 p. m. and at 5 p. m.. Following the injections a brief improvement seemed to set in, but the patient did not regain consciousness. The bicarbonate content of the plasma was 16.6 at 2.30 p. m., 11.2 millimols at 3.30 p. m., and 10.1 millimols at 9.30 p. m., 2 hours before death supervened. Analysis of the blood for acetone bodies gave a negative result.

At autopy the liver was found to be small, greyish yellow, and cirrhotic.

Case record No. 49. Acute yellow atrophy of the liver.

(Schmitt, F. and Basse,[193] *W., Deutsches Arch. f. klin. Med.,* 180: *22, 1937).*

A woman, aged 57, had been taken ill a fortnight before admission to the University Clinic, Göttingen, with cold shivers, vomiting and icterus. When admitted to the hospital she was unconscious with pronounced Kussmaul respiration and small, rapid pulse. There was marked jaundice of the skin, and the urine gave a strong bilirubine reaction. Analysis of the blood showed distinct acidosis, the bicarbonate content of the plasma being reduced to 14.1 millimols.

Death supervened 9 days after admission. The autopy showed typical yellow atrophy of the liver.

2. Acute Febrile Bile Duct and Liver Affections.

In acute febrile bile duct and liver affections a considerable acidosis will sometimes occur. Its pathogenesis is still obscure, but probability favours the assumption that the acidosis is part of a so-called »hepato-renal syndrome«, a term used especially by the Nonnenbruch school of physicians, and having reference to a supposed connection between the function of the liver and that of the kidneys. In serious bile duct and liver diseases (especially, it would seem, in the presence of obstructive jaundice) a very substantial reduction of the renal function in the shape of a reduced power of concentration and oliguria may thus occasionally be seen. It is possible, as assumed by Nonnenbruch,[151] that the renal insufficiency is the direct cause of the development of the acidosis.

In 1935 the author[89] published a case of obstructive jaundice with purulent cholangitis, in which a considerable acidosis occurred, and in which treatment with isotonic sodium bicarbonate solution brought about a very marked clinical improvement (Case record No. 50). In Denmark Zacho[234, 235] has recently collected a number of cases of that syndrome. Even though this form of acidosis is comparatively rare, it is, as pointed out by the author and by Zacho, unlike the acidosis of hepatic coma, of considerable therapeutic interest, as the treatment with isotonic sodium bicarbonate solution seems to have a decidedly favourable effect on its course.

Case record No. 50.
Purulent cholangitis. Obstructive jaundice.

(Own observation,[89] *Ugesk. f. Læger,* 97: *1212, 1935).*

A woman, aged 68, was admitted to Department D of the Bispebjerg Hospital in Copenhagen in a very low condition, with symptoms of obturescent choledochus stone and purulent cholangitis. Choledocholithotomy was performed and hepatic drainage established. The first 6 days after the operation a total of 10 litres of 5 p. c. glucose solution was given, (partly with and partly without sodium chloride). In spite of this treatment the patient was still somnolent and semi-conscious, and the diuresis very scanty, with a reduction of the urea clearance to 0.5 p. c.. Analysis of the plasma at this stage showed the presence of a moderate acidosis (17.1 millimols of bicarbonate), while the chloride concentration was normal, (11.1 millimols). For the following 5 days 1 litre of isotonic sodium bicarbonate solution was injected intravenously per day, after which the acidosis was entirely relieved (31.0 millimols). Following this treatment the clinical condition appreciably improved, the patient becoming mentally natural and eating with a good appetite. During the treatment the diuresis rose to 1500 c. c. daily at the same time as the renal function was improved (clearance 9 p. c.).

In the following period recovery progressed steadily. 10 days later the renal function had increased to 35 p. c. and after a couple of weeks to 45 p. c..

The patient was discharged quite well.

Case record No. 51. Hepatic abscess.

(Zacho, A.,[235] *Acta chir. Scandinav.,* 88: *383, 1943).*

A farmer, aged 58, who had previously been in good health was admitted to the District Hospital of Roskilde on February 26, 1941. He had been taken ill 3 weeks before admission with the temperature elevated to 39.2°, cold shivers, pains in the back, and a dry cough. There had also several times in the day been griping pains in the upper part of the abdomen, not accompanied by vomiting. A week after the illness began the patient noticed that the urine became dark-coloured, while the stools were of normal appearance. The condition gradually became worse, and for the last week before admission the patient had hardly eaten anything.

When admitted to the hospital on February 26, the patient was somewhat low and slightly icteric. The tongue was dry and coated, the temperature had risen to 38.5°. The liver was felt to be moderately enlarged, the edge extending 4 cm below the right costal margin. The urine contained bile pigment but neither sugar nor

albumen. The urine diastase values were normal, the blood urea concentration was 46 mg p. c..

In the course of the following 10 days the condition was gradually aggravated. The fever was intermittent, the temperature ranging from 36.0°—40.2°, there were attacks of profuse perspiration, and the patient was tired and seemed somewhat semi-conscious. Fluoroscopic examination of the abdomen on March 7, showed a considerable enlargement of the liver and upward displacement of the right half of the diaphragm. The respiration at this stage assuming the character of »grosse Athmung«, a determination was made of the bicarbonate content of the plasma which revealed the presence of a moderate acidosis (11.3 millimols), while the blood urea value was found to be increased to 100 mg p. c.. On March 9, therefore, 1800 c.c. of isotonic sodium bicarbonate solution were given intravenously, after which the bicarbonate concentration rose to normal (29.0 millimols), while simultaneously the condition improved somewhat. This improvement was only brief, however, and in the following days the patient again grew worse, more semi-conscious and restless. The temperature was still elevated, the tongue dry, and the abdomen meteoristically distended with a distinct mass in the upper section corresponding to the site of an enlarged liver; stethoscopy of the lungs revealed dullness and impaired respiration over the base of both lungs.

On March 12, the bicarbonate concentration of the plasma was again determined; it showed that the acidosis had recurred (10 millimols). On March 13, therefore, 1 litre of isotonic sodium bicarbonate solution was given subcutaneously, and again it was possible by this treatment to obtain a distinct but brief improvement. In spite of a repetition of the injection on March 16 (1.4 litres) the condition was steadily aggravated, the diuresis decreased, and signs appeared of an increasing uremia (blood urea concentration 246 mg p. c.). The respiration gradually became irregular, at times of the Cheyne-Stokes type. Death supervened on March 20.

Upon autopsy the liver was found to be considerably enlarged with numerous larger and smaller communicating abscess cavities filled with pus in the upper half of the organ, and with a thrombosis as thick as a pencil in the hepatic veins of the liver. The rest of the liver tissue was the site of marked parenchymatous degeneration. Upon microscopic examination the kidneys showed only slight changes.

3. Acidosis in Thyreotoxicosis.

The occurrence of acidosis in thyreotoxicosis has been described by several investigators, thus by Walinski and Herzfeld,[223] who in 6 cases of uncomplicated Graves' disease

found the bicarbonate content of total blood reduced to an average of 14.2 millimols (corresponding to a calculated plasma bicarbonate value of 17.1 millimols), and by Coelho,[26] who in 8 out of 40 cases found a distinct acidosis (in 2 patients a reduction to 16.5 millimols). In contrast herewith Altenburger and Böger,[5] v. Sköld[200] and Bartlett,[13] on examination of a total of 45 patients with Graves' disease of which several were seriously ill, only found certain reduction in 2 cases (19.6 and 18.5 millimols), while the plasma bicarbonate values in the other cases were normal, though often at the lower limit of the normal range. On the basis of these data it must be regarded as established that in thyreotoxicosis a moderate and sometimes perhaps a more serious acidosis may occasionally occur. Thorough investigations on this form of acidosis are as yet lacking, though according to Somogyi[13] there often seems to be a considerable ketonemia as a concurrent cause of the development of the acidosis.

4. Acidosis in Acute Suppurative Otitis Media in Infants.

In severe cases of acute suppurative otitis media in children under 1 year old acidosis occurs as a very frequent complication which often attains serious degrees. In spite of the frequency of the acidosis the literature only contains few reports of this form. The author, however, is anxious to point out the significance of this otogenic acidosis in children, since its presence may give rise to serious error of diagnosis (Kirk[103]), a fact which will be discussed in more detail below.

The first publication concerning the occurrence of acidosis in acute otitis media in children was issued by Hartmann[65] in 1928; in this publication and in a later report from 1938 (Hartmann and co-workers[69]) a total of 34 cases of acute otitis media and mastoiditis is recorded, 30 of which were complicated with acidosis (of these, 21 with acidosis of a severe degree) and no small number with uremia. In a large number of the patients the lactic acid concentration of the blood was found to be substantially increased. Of the treated children 30 died, i.e. 88 p.c.. Thus the infections were very serious, and in many cases the clinical picture bore a great resemblance to the symptoms in acute gastro-enteritis. The therapy adopted was, besides operation, the administration

of saline, glucose solution, 5 p.c. sodium bicarbonate solution and 1/6 molar sodium lactate solution. Of these treatments the administration of bicarbonate seemed occasionally to cause at any rate a temporary amelioration of the dyspnea and the semi-consciousness. Hartmann expresses his view of the significance of the bicarbonate therapy in the following passage: »Because of the frequent marked loss of base bicarbonate from the body intravenous administration of sodium bicarbonate is often indicated and may at times be a lifesaving measure,« a view which, however, in the author's opinion, must be compared with the great mortality in the cases reported if we want to arrive at a true estimate of the results of the treatment. In the cases of acidosis published in 1938 the bicarbonate therapy seems to have been abandoned in favour of parenteral sodium lactate treatment, which however is not seen to have had any conclusive influence on the mortality, even though an essential rise in the serum bicarbonate concentration was often gained. The rise was, however, frequently less than had been calculated according to the lactate dose given, which is presumably due to the fact that the lactate combustion must have been imperfect in these very sick children (see pp. 37 and 73).

In a publication dating from 1933 Csapó and Kerpel-Fronius[28] likewise mention severe cases of acute otitis media in infants complicated with acidosis and uremia. As in Hartmann's group of patients, a good effect was obtained in some of these cases by the administration of 4 p.c. sodium bicarbonate solution, since it was occasionally possible to relieve the acidotic coma by this treatment. As a rule, however, the improvement was only temporary, the outcome being fatal in spite of the treatment.

The same publication records investigations on the nature of the acidosis. From the analyses it appears that the acidosis is predominantly due to accumulation of organic acids (organic acidosis) but that there is also frequently an increase in the phosphate values. While the rise of the phosphate values must be assumed to be due to oliguria as a result of dehydration, the cause of the considerable rise of the organic acids has not been elucidated with certainty. Csapó and Kerpel-Fronius state that the accumulation of acid must be supposed to originate from the action of the bacterial toxins on the intermediate metabolism. This supposition seems probable to the author (see p. 122), who would, however, like to

add that the bacterial effect might also be conceived to assert itself in a more indirect manner, through toxic substances being produced by the tissue cell destruction due to the infection. Investigations in this field are, however, entirely lacking as yet, but would perhaps yield a good return. As the bacterial toxins are presumably in great part absorbed from the cavum tympani and the mastoid process (Hartmann[65]), analyses of the composition of the secretion from the ear may enter as an element into the investigations on the etiology of this form of acidosis.

In most cases of acute suppurative otitis media in infants other factors must, however, also be supposed to contribute to the development of the acidosis. Thus the circulatory insufficiency and anoxemia caused by the intoxication will bring about an accumulation of lactic acid due to the imperfect oxidation, just as the toxic destruction of the tissue will give rise to an abnormal production of organic and inorganic acids. In most of the cases in which the acute otitis media is accompanied by marked gastro-intestinal symptoms, especially diarrhea, there is, moreover, the possibility that acidosis will develop through the loss of total base and of bicarbonate. It agrees with this that reduced total base values were not rarely found in Hartmann's group of patients.

The most striking acidotic symptoms in otogenic acidosis are dyspnea and the effect on consciousness. The considerable relief of the dyspnea and the greater alertness which is often observed after injection of a bicarbonate solution plainly indicates this connection. In many cases, however, the acidosis, even in rather severe degrees, seems not to give appreciable clinical symptoms, a fact which, as previously mentioned, is well known from other acidotic conditions in children. As the bicarbonate concentration of the serum may sometimes be reduced to 3—5 millimols, it must, on the other hand, be supposed that the acidosis may occasionally contribute directly to the fatal outcome. As a rule, however, death is probably due to the direct action of the bacterial toxins on the central nervous system and the circulatory organs. In accord herewith autopsy often shows pronounced parenchymatous degeneration of the organs (Hartmann[65]. Csapó and Kerpel-Fronius[28]).

On the basis of clinical investigations on this form of acidosis the author in 1943 called attention to a fact of special significance, viz. *that the acidotic dyspnea (hyperpnea) in*

acute suppurative otitis media in infants may be mistaken for pneumonic dyspnea. There is therefore the possibility that it is erroneously diagnosed as pneumonia whereas the dyspnea is in reality due to an acute otitis media with acidosis. The difficulty of seeing the eardrums in children under one year old and the frequent simultaneous occurrence of pneumonia and otitis media also contribute to the latter affection being overlooked, an error which may have a fatal effect, since the patients are then deprived of the effective help of an incision of the tympanic membrane. In the author's opinion it quite frequently happens that as a consequence of the acidosis infants suffering from otitis media die with a wrong diagnosis.

In the author's Hospital Department 20 infants suffering from acute otitis media were treated in the period 1941—43 (see Table 8).

In all the children there were signs of acidosis, which in 5 cases could be designated as mild, in 5 as moderate, and in 10 as severe. Of the 20 children 4 died. Even though the children seem on the average to have been somewhat less ill than in Hartmann's group of patients, they were in all cases seriously ill; 12 of the cases were complicated with pneumonia, mastoiditis, or meningitis. In cases taking a favourable course spontaneous relief of the acidosis was observed during recovery; this spontaneous rise in the plasma bicarbonate concentration generally set in fairly soon after a successful incision of the tympanic membrane simultaneously with an appreciable abatement of the dyspnea.

For the treatment of the acidosis the author used subcutaneous or intrasternal injection of isotonic sodium bicarbonate solution in those cases in which the children were highly dyspneic or very ill, or in which the serum bicarbonate values were much reduced. This treatment, *which does not hitherto seem to have been employed,* as will appear from the cases recorded below, has a very favourable effect on the dangerous condition. It should, however, as rule only be regarded as a supplementary therapy to the operation (myringotomy, mastoidectomy). In a disease such as acute otitis media, in which the acidosis may either be aggravated spontaneously by an increased production of organic acids, or decrease on account of the combustion of the acids, it will often be desirable to check the bicarbonate values in the serum by repeated determinations in the course of the disease.

Table 8.

Bicarbonate content of serum in infants with acute suppurative Otitis media.

Own observations.

Case history No.	Initials	Sex	Age in months	Serum bicarbonate millimols per l	Complications	Result of treatment
370/43	L. J.	girl	3	3.6	Mastoiditis	died
1094/42	K. C.	boy	4	6.7		recovered
1641/42	J. N.	boy	8	7.0		recovered
644/43	E. K.	boy	7	9.0	Pneumonia	died
154/43	K. P.	boy	8	9.2		recovered
355/43	E. B.	girl	5	9.5	Pneumonia	recovered
443/43	B. N.	boy	8	10.0	Mastoiditis	recovered
354/43	H. Ø.	boy	9	10.3	Pneumonia	recovered
458/43	B. N.	girl	8	10.5	Pneumonia	recovered
347/43	E. J.	boy	2	11.2	Pneumonia	recovered
93/43	S. G.	boy	10	13.0	Meningitis otogenica	died
1583/43	A. H.	girl	5	13.4		recovered
1087/42	A. J.	girl	4	14.0	Pneumonia	died
1436/43	J. J.	boy	5	15.2		recovered
1599/42	O. L.	boy	8	15.3		recovered
839/42	G. L.	girl	1	17.3		recovered
1588/41	B. L.	girl	6	17.4	Meningitis otogenica	recovered
1069/42	B. P.	boy	7	17.5	Pneumonia	recovered
163/43	V. A.	boy	9	17.5	Pneumonia	recovered
361/43	J. J.	boy	5	18.6		recovered

The first case record shows a serious case of acute otitis media and pneumonia, with severe acidosis. An essential relief of the dyspnea and improvement of the general condition was achieved after treatment with isotonic sodium bicarbonate solution.

Case record No. 52.
Acute suppurative otitis media. Pneumonia.

(Own observation. Nord. med., 25: 309, 145).

On August 2, 1942 a boy, 4 months old, was admitted to the Medical Department of the Holstebro District Hospital. He had been taken ill 3 days before admission with mounting temperature and increas-

ing dyspnea. On the morning of the day of admission the temperature was 40.5°. 10 hours before admission treatment with sulphathiazol had been instituted.

Upon admission to the hospital the child was moderately ill, very dyspneic with a respiration rate of 48. The temperature was 40.1°; there was no cyanosis but pronounced dryness of the tongue. Stethoscopy of the lungs revealed scattered rales and ronchi over both lungs. Upon otoscopy the left ear drum was found to be mildly inflamed but not bulging.

Treatment with sulphathiazol injections was at once instituted; in addition, because of the very high temperature, a tepid bath of 28° was given several times. In spite of this the condition grew worse in the course of the following day, and on the morning of August 5 the child had an attack of convulsions. Examination of the ears at this stage showed injection and bulging of the left ear drum and slight injection of the right drum. Hence bilateral incision of the tympanic membranes was performed with evacuation of plenty of pus from the left ear and a sparse secretion from the right ear. In the following hours the child was very low with cyanotic greyish yellow colour, cold extremities, rapid pulse (174) and deep and rapid respiration (frequency 74). Because of the marked dyspnea the bicarbonate content of the serum was determined and showed the presence of a severe acidosis (6.7 millimols). Immediately afterwards 200 c. c. of 1.3 p. c. sodium bicarbonate solution were given subcutaneously, and this treatment was repeated 4 hours later. Already after the first bicarbonate injection an appreciable improvement of the condition was observed. The next morning (August 4) the cyanosis had disappeared, the pulse rate was decreasing and the respiration less deep but still distinctly rapid (64—72). The temperature was 39.3°, and there was a copious purulent secretion from both ears. In the afternoon the bicarbonate determination was repeated; it showed a rise to 16.2 millimols. After this 200 c. c. of 1.3 p. c. sodium bicarbonate solution were given, whereupon a further improvement of the condition set in. The respiratory frequency in the hours that followed decreased to 42, the pulse rate to 144, while in the course of the evening and the following night the temperature dropped to normal values (37.0°).

During the following days the improvement continued and upon analysis on August 6 the bicarbonate concentration of the serum showed normal conditions (21.0 millimols). During the rest of the stay there were no further otogenic or pulmonary attacks, and the child was discharged in good health on September 10.

The following case illustrates the close connection between acute otitis media and acidosis. During the treatment of a bilateral otitis media with incision of the tympanic mem-

branes and the administration of sodium bicarbonate solution the acidosis was relieved only to appear again 4 days later following a recurrence of the ear symptoms.

Case record No. 53. Acute suppurative otitis media.

(Own observation. Nord. med., 25: 309, 1945).

A boy, 8 months old, was admitted to the Medical Department of the Holstebro District Hospital on December 14, 1942. He had been taken ill 2 days before admission with catarrhal symptoms. Shortly after the beginning of the illness dyspnea had set in, and on the day of admission it was so pronounced that the parents called in a physician.

Upon admission the child was very low with dilatation of the nostrils on inhalation. The respiration rate was 90, the pulse 152, the temperature 39.6°. Scattered rales were heard over both lungs. Otoscopy revealed a bilateral acute otitis media, and analysis of the blood showed the presence of a severe acidosis, the bicarbonate concentration of the serum being reduced to 7.0 millimols.

Incision of the tympanic membranes was immediately performed with evacuation of pus on both sides; in addition sulphathiazol treatment was instituted, 2 g of sulphathiazol being given in a single dose. Finally 150 c. c. of 1.3 p. c. sodium bicarbonate solution were injected subcutaneously. In the course of the next 12 hours the temperature fell to normal (37.1°), while at the same time the dyspnea decreased appreciably (respiration rate 66). The following day (December 15) the analysis of the blood was repeated and showed a rise of the bicarbonate value to 11.1 millimols. Since the acidosis was thus still rather pronounced, 150 c. c. of isotonic sodium bicarbonate solution were again injected subcutaneously. An analysis of the blood performed the next day (December 16) showed that the acidosis had been relieved (21.3 millimols).

During the following days the temperature remained normal. On the evening of December 20, however, it mounted to 38.8°. Examination of the ears showed plentiful secretion of pus from the left ear whereas the incision on the right side was closed with marked bulging of the ear drum. At this stage the child was somewhat dyspneic, and analysis of the blood showed that following the recurrence of the symptoms of otitis, acidosis had again set in (15.3 millimols). Rightsided myringotomy was then performed with evacuation of pus under pressure. In addition 2 g of sulphathiazol were given by mouth, and 75 c. c. of isotonic sodium bicarbonate solution subcutaneously. In the course of the next 5 hours the dyspnea decreased, and the temperature again fell to normal. A bicarbonate determination made on December 22 showed normal values.

As there was still during the following days a tendency to closing of the incision, the child was transferred on December 23 to the Ear Department of the Hospital from which it was discharged well on January 2, 1943.

5. Acidosis in Other Serious Infections and Septic Conditions.

In other infections than the acute suppurative otitis media a severe acidosis is also often seen in children. In many cases of serious infection in adults, on the other hand, the bicarbonate content of the plasma seems to be normal (Whitney[231]), though in severe septic and pyemic diseases, thus in puerperal fever with peritonitis, a considerable reduction of the bicarbonate concentration has also been observed (Gaessler[51]). Bøggild[20] too has in several cases demonstrated the presence of acidosis in suppurative peritonitis, and in a preliminary report has published favourable results of a treatment with isotonic sodium bicarbonate solution. During an influenza epidemic in Cincinnati in 1920 Hachen and Isaacs[59] examined 20 patients in a very low condition; in 4 of the cases the bicarbonate concentration of the plasma was reduced to less than 20 millimols (19.5, 19.1, 16.5, and 10.4). The pathogenesis of the acidosis has not been more closely investigated, but it must be supposed that the same factors are concurrent causes as were mentioned under otitis media.

Some of the infections belonging to this group form a transition to the infectious secondary gastro-enteritis in children, while other instances of severe sepsis must rather be classed with the premortal cases of acidosis. A number of cases of acidosis in severe infections in children are mentioned in the publication from 1938 by Hartmann and coworkers[69] quoted in the last section.

In the period 1942—44 the author made determinations of the bicarbonate content of the serum in 18 cases of severe pneumonia in children less than 1 year old. The results of these analyses are given in Table 9 and show that acidosis is a frequent occurrence in pneumonia in infants.

Below is given the record of a case of acidosis with pneumococcus pneumonia, which took a favourable course.

Table 9.

Bicarbonate content of the serum in 18 cases of severe pneumonia in children.

Own observations.

No. Case history	Initials		Age in months	Serum bicarbonate Millimols per l.	Result of treatment
316/42	E. M.	girl	11	7.7	recovered
1134/44	K. M.	boy	3	7.9	died
625/44	T. P.	boy	7	9.0	died
1244/44	B. N.	girl	6	9.5	recovered
44/43	K. S.	girl	8	10.0	recovered
447/43	K. V.	boy	3	10.0	died
809/44	P. J.	boy	2	10.8	recovered
274/43	K. S.	girl	8	11.2	died
651/43	N. K.	girl	10	12.0	died
423/42	P. E.	boy	5	14.6	died
784/43	K. S.	boy	9	14.7	died
722/44	A. N.	girl	1	14.7	recovered
450/43	P. K.	boy	5	14.9	died
674/44	S. A.	girl	7	15.4	died
899/43	S. J.	boy	6	17.0	recovered
144/44	A. K.	girl	4	17.5	recovered
11/43	B. C.	boy	10	23.7	recovered
231/43	K. A.	boy	2	26.1	recovered

Case record No. 54.
Pneumococcus pneumonia.

(Own observation).

A girl, 6 months old, was taken ill on October 1, 1941 with a cough and stethoscopic signs of bronchitis. 2 days later the condition was aggravated, the temperature mounting to 39.7° and the child vomiting several times. At 10 p. m. the family physician was called in; he diagnosed right-sided pneumonia and instituted treatment with sulphapyridin. At 1 o'cl. in the night the child suddenly grew limp and apparently ceased to breathe. After 5—10 minutes the condition improved again, but as the child was still very ill and had high fever (40°) she was admitted at 3 a. m. to the Medical Department of the District Hospital of Holstebro.

When admitted the child was somewhat low, with congested face. There was no cyanosis but considerable dyspnea and dilatation of

the nostrils on inhalation. Over the lower part of the right lung numerous rales were heard both on the anterior and the posterior surface of the thorax. There were no clinical signs of meningitis, and the lumbar fluid was clear and contained no cells. On examination of expectorate obtained from the larynx the presence of pneumococci of type 6 was demonstrated. One hour after admission 40.000 units of type 6 rabbit pneumococcus serum were injected intravenously in the saggittal sinus, and at the same time treatment with sulphathiazol was instituted. In the course of the night the child passed 4 small fluid stools. No further attacks of collapse occurred.

On the following day the condition was unchanged. The temperature was still increased to between 40° and 40.5°, the respiration rate to between 60 and 80. In view of the considerable dyspnea a determination of the bicarbonate in the plasma was made in the morning; it showed the presence of a severe acidosis (9.5 millimols of bicarbonate). 100 c. c. of isotonic sodium bicarbonate solution were therefore given subcutaneously (and further 40.000 units of pneumococcus serum intramuscularly). In the course of the day the child passed one natural stool.

The next morning (October 4) the temperature was normal, 37.5°. The dyspnea had disappeared (respiration rate 40) and the condition seemed somewhat improved. Analysis of the blood showed an increase in the bicarbonate concentration of the plasma to 12.3 millimols.

On October 5 the bicarbonate value was normal (20.0 millimols). The child drank well and seemed to be doing well. The further course was uneventful, and the child was discharged recovered on October 15.

K. Premortal Acidosis.

Even though a more consistent determination of the serum bicarbonate concentration in the clinic would make it possible to delimit more forms of acidosis than those already mentioned, it can hardly be expected that considerable acidosis could be found to any great extent in other affections. This consideration does not apply, however, to moribund patients, in whom acidosis is no rare finding. The occurrence of the agonal acidosis has been demonstrated almost simultaneously by the American, Whitney,[231] and the Danes, Sonne and Jarløv.[201] Whitney's investigations comprise 40 patients. In one of these only was the bicarbonate content of total blood normal, while in 37 acidosis was shown to be present, which in some

cases reached such extreme degrees that it may have been the real cause of death (2—5 millimols). In two patients who had presented symptoms of gastric tetany before death, the bicarbonate values were above normal. The blood samples analysed were collected by heart puncture immediately after the supervention of death. In many of the samples the urea content was found to be much increased (agonal uremia). By determining the bicarbonate concentraction of venous blood before the supervention af death in some cases Whitney was also able to show that the premortal acidosis was as of rule of short duration (from a few days to a few hours) and most frequently developed after the premortal rise in the temperature had set in.

Sonne and Jarløv's publication is of importance as containing the first published case record of premortal acidosis with a description of the patient's condition, and because of the special emphasis laid on the significance of the agonal element for the causation of the acidosis. In the later literature there are only some few reports of the finding of acidosis in moribund patients, thus Lipetz[119] in 3 agonal cases found a reduction of the bicarbonate content of the serum to 9.0, 5.7, and 8.5 millimols. Several of the children with severe infectious diseases examined by Hartmann[65] and co-workers[69] may also be termed moribund, as death supervened a few hours after the taking of the samples.

Concerning the etiology of the agonal acidosis it may be mentioned that in 1932 Becher, Enger, and Herrmann[15] found a great increase in the amount of ether-soluble acids in the blood immediately before death and after the supervention of death. That there is often premortally a considerable increase in the content of amino acids in the blood has been shown by Becher and Herrmann[14] by means of Folin's colorimetric method, and was confirmed by the author[90] (1935) and by Fabricius-Hansen[44] (1945) by a gasometric technique. The increase of amino acid in the plasma is presumable due to autolytic destruction of the tissue; by the autolysis other acid products of significance for the development of the acidosis may possibly also be formed. As previously stated (see p. 125), the amino acids themselves hardly contribute much towards this, since with some few exceptions they do not supplant the bicarbonate.

Comprehensive researches on the agonal acidosis were carried out by Fabricius-Hansen[44] at the author's Hospital Depart-

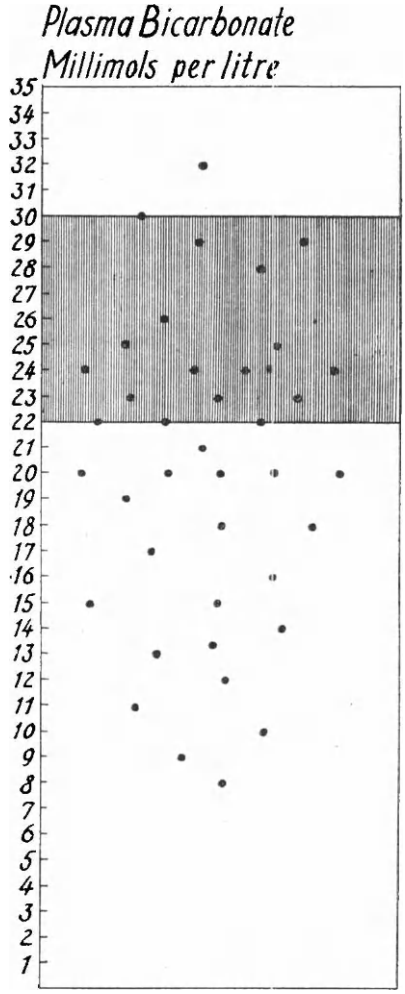

Fig. 17. The bicarbonate concentration of plasma in agonal conditions. The shaded section of the figure denotes the area of normal values. After Fabricius Hansen, I., »Investigations on the Agonal Acidosis«.

ment in the years 1941—44. Besides measurement of the pH and bicarbonate analysis the investigation comprised determinations of the total base, chloride, phosphate, sulphate, protein, lactic acid, amino acid, urea, and residual nitrogen content of the plasma. In addition the total acetone, pyruvic

acid, and guanidine concentration in total blood was determined, and gasometric hemoglobine determination and measurement of the degree of oxygen saturation was carried out. In 25 out of 38 cases the pH value was found to be reduced to less than 7.20, in 18 of the cases to less than 7.10. The average agonal pH value was 7.11, the lowest observed value 6.66. Compared with this the bicarbonate reduction was less striking (see Fig. 17), a finding which only partially confirms Whitney's observations. As a specially characteristic change in the agonal acidosis may be pointed out the increase in the lactic acid content of the plasma, the average value being about 8 times higher than usual. In contrast herewith the content of keto-acids in the blood was only sligthly or not increased, whereas the concentration of other organic acids often showed a distinct rise. As in Whitney's group of patients the blood urea values were as a rule much increased, so that in this form of acidosis too the uremia must be termed a frequent complication. A review of the average values found in the analysis of samples collected in agonal conditions will be found in Table 10, from which it appears that the increase in the values for lactic acid, undetermined organic acids, and sulphate in the plasma must be regarded as the chief cause of the bicarbonate reduction. In this form of acidosis the accumulation of free carbon dioxide in the blood seems to play an important role for the lowering of the pH values (see footnote p. 13). The presence of circulatory insufficiency, shock, reduced pulmonary ventilation, impaired renal function, autolytic destruction of tissue, and terminal infection are presumably of essential significance for the occurrence of these changes in the blood, but changes in the intermediary metabolism may perhaps also be a concurrent cause.

The mutual significance of these factors for the development of agonal acidosis is often difficult to elucidate. In this connection it should be pointed out that the agonal acidosis, even in very different groups of diseases, has numerous features in common, a fact that is a further justification for the delimitation of this form of acidosis.

The investigations on agonal acidosis here communicated are, in the author's opinion, of considerable theoretical interest, since they yield an important contribution to the understanding of the changes in the organism that precede death, a field of clinical medicine which is as yet little

Table 10.

Electrolyte content, pH, carbon dioxide tension and content of various nitrogenous substances in the serum under agonal conditions.

After Fabricius Hansen, I., »Investigations on the Agonal Acidosis«.

	Normal values	Values found under agonal conditions			
	mean	mean	minimum	maximum	
Total base	158.1	166.0	145.2	192.0	milliequiv.
Total carbon dioxide	28.4	22.5	9.6	33.4	»
Bicarbonate	27.0	20.5	8.1	31.5	»
Chloride	106.0	99.9	81.1	120.6	»
Sulphate	1.0	4.4	0.7	16.4	»
Secondary phospate	2.1	3.5	1.2	6.0	»
Primary phosphate	0.3	1.1	0.2	3.2	»
Protein	18.0	14.7	9.7	19.5	»
Lactic acid	1.4	10.9	3.2	21.3	»
Keto-acids	0.2	1.1	0.1	6.5	»
Pyruvic acid	0.1	0.3	0.1	0.6	»
Non-determined acids	2.2	9.5	—5.7	22.4	»
Total acid	154.3	156.0	133.9	184.0	»
pH	7.38	7.11	6.66	7.51	
Carbon dioxide tension	42.7	73.4	23.0	168.5	mm
Residual nitrogen	33.8	103.8	26.0	374.0	mg p.c.
Urea nitrogen	15.8	76.9	14.1	301.0	»
Amino acid nitrogen	6.5	12.4	4.0	34.0	»
Creatin + creatinine	6.3	11.1	4.0	34.0	»
Guanidine	0.2	0.1	0.1	0.3	»

investigated. Our scanty knowledge of the biochemistry of the agonal condition is quite understandable considering the natural reticence shown in the examination of moribund patients. However, the greatly increased possibilities of the effective fighting of disease provided of recent years by the introduction into therapeutics of the sulphathiazol preparations, penicillin, and similar drugs, render it desirable, in the author's opinion, to direct greater attention to the premortal condition. Thus it cannot be excluded that a therapy aimed at the pathophysiological components in the agonal condition would be able to prevent the supervention of death for so many hours that the drugs used against the primary disease (e. g. penicillin in septic infections) would have time to exercise their effect. Since, as mentioned above, the aci-

dosis in a number of moribund patients seems to be a conspicuous feature of the clinical premortal condition, parenteral treatment with bicarbonate may sometimes be indicated under these circumstances. Such a therapy has occasionally been applied in the author's hospital department, but the results gained are as yet too sparse to warrant further discussion.

L. Chronic Acidosis.

1. Renal Rickets. 2. Renal Osteomalacia. 3. Osteomalacia following Prolonged Ingestion of Acidotic Drugs. 4. Osteoporosis in Persistent Hepatic Fistulas.

When the acidosis is present for a long period, perhaps for years, severe changes of the bones in the form of decalcification (osteoporosis) and reduced bone growth not rarely occur. These changes most frequently take place in connection with chronic affections of the kidneys, in which prolonged acidosis, as already stated, is quite frequently met with. If skeletal changes arise before the growth is completed, as is as a rule the case, the affection is classified as renal dwarfism and renal rickets; in fully developed individuals, on the other hand, the term osteomalacia is used.

Renal rickets and osteomalacia especially occur in congenital obstructive affections of the urinary system, thus when there is an abnormal valve formation at the internal orifice of the urethra, in strictures of the ureters, and in various developmental anomalies. As a result of the obstruction of the urinary tract considerable hydronephrosis with reduction of the renal tissue to a shell round the distended renal pelvis is often observed. Some few cases have been observed in congenital renal cysts. The disease may also develop in association with acquired renal affections. It is often accompanied by serious urinary infection.

The pathogenesis of the skeletal changes is not yet fully cleared up. Previously attention has especially been directed towards the changes in the serum calcium and serum phosphate values. In renal rickets, as altogether in more serious renal insufficiency, it is usual to find increased phosphate values and reduced calcium values of the serum, but normal values may also be seen in this affection. On the other hand,

in all the cases of renal rickets in which more detailed investigations have been made it has been possible to demonstrate a conclusive reduction of the bicarbonate content of the plasma, i.e the presence of an acidosis. Since it has been established experimentally that the administration of substances with an acidotic effect causes an increased excretion of calcium with removal of calcium from the bones for the neutralisation of the ingested acid, it seems natural to assume that the osteoporosis in renal rickets and osteomalacia is likewise due to a decalcification caused by the acidosis (György,[58] Schoenthal and Burpee[194]). A particularly instructive case of osteoporosis in chronic acidosis has been described by Nielsen[150] (1941), who observed marked osteomalacia in a woman 34 years old, who for 3-4 months had daily taken 12 g of mandelic acid and 4 g of ammonium chloride (Osteomalacia acidotica). In cases of persistent bile fistulas with acidosis caused by loss of alkali, typical osteoporotic changes of the bones are also occasionally seen (Düttmann[39]), which, however, are perhaps due to imperfect absorption of fat-soluble vitamins from the intestinal tract. The osteoporosis of renal rickets can be clinically demonstrated by Roentgen photographs of the bones and by the skeletal deformities (deformities of the vertebral column, thoracic changes with pigeon breast and rachitic rosary, affections of the extremities in the shape of genu valgum and genu varum) caused by the decalcification. Osteoporosis is not rarely accompanied by considerable pains in the bones which may necessitate daily morphine injections (Hagens[60]). Often clinical signs of uremia are observed, especially following aggravation of the reduction of the renal function.

A knowledge of the bearing of the acidosis on the development and continued progress of the disease is of great importance, an essential clinical improvement being frequently possible through alkali treatment of the acidosis. The administration of alkali will not rarely relieve the patients of pain, and with continued treatment it is often possible to show roentgenologically that the calcium content of the bones again becomes normal. More severe degrees of acidosis may necessitate an initial treatment with intravenous injection of bicarbonate. As a rule, however, the administration of alkali powders by mouth is sufficient (about 10 g of sodium bicarbonate per diem). It has also occasionally been possible by treatment with calcium preparations and irradiated ergosterol

to arrest the osteoporosis. Prophylactically an early surgical treatment of the congenital affections of the urinary ducts may possibly in some cases prevent the development of chronic renal affections and acidosis.

V

Technique for the Determination of the Bicarbonate Content of the Plasma or the Serum.

The most convenient method of determining the bicarbonate content of the plasma or the serum is by the gasometric determination with Van Slyke's manometric apparatus. This apparatus was introduced in its present form in 1927[217] and in the United States, on account of its great clinical and physiological applicability and its convenience in handling, it has in the main superseded an earlier model[219] (1917), the so-called volumetric apparatus. According to the author's experience the motor-driven manometric apparatus is decidedly to be preferred for hospital departments as it is much more convenient in the working than the volumetric apparatus and unlike the latter permits bicarbonate determination by micro-analysis (0.1 c. c. of serum), a determination which, as previously stated, is of the greatest significance in the treatment of gastro-enteritis in children.

1. Instructions for Use of Van Slyke's Apparatus

The gas analysis apparatus (see Fig. 18) consists of an extraction chamber connected with a closed graduated manometer tube and a levelling bulb. The chamber is calibrated at 0.5, 2.0, and 50.0 c.c.*) and is closed at top by means of a ground glass cock (A) with two bores, one of which connects the chamber with a glass cup, while the other opens into a curved capillary tube (Fig. 21). The glass cup serves for the delivery of samples and reagents into the chamber. The removal of these from the chamber takes place by suction through a short glass tube the point of which is provided

*) For certain other analyses it is an advantage to have also a calibration at 10 c.c. volume.

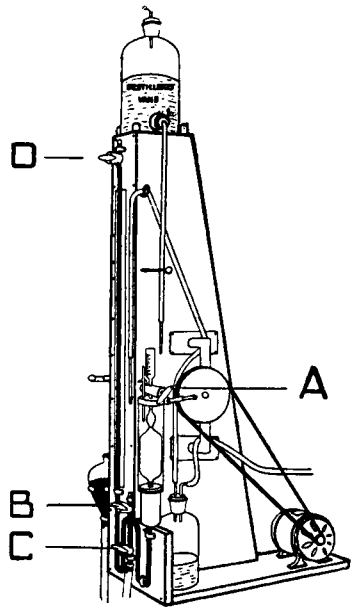

Fig. 18. Van Slyke's manometric gas analysis apparatus.

with a rubber ring*) so that the tube can be pressed firmly down against the bottom of the cup. The suction is carried out with a water suction pump; for the collection of drawn off mercury a one litre flask in inserted into the rubber tube. The communication between the chamber and the rest of the apparatus is through a thick-walled rubber tube. The rubber connection permits shaking of the chamber by a motor-driven metal wheel with an excentric shaking device with a velocity of 300—400 shakes per minute.

In the analysis the amount of the extracted gas is determined by reading the pressure which the gas exerts at a known volume. To facilitate the reading on the manometer tube the latter is mounted on a sheet of mirror glass or a strip of frosted glass. At the adjustment of the fluid meniscus to the divisions in the extraction chamber it is an advantage

*) Rubber rings for mounting on suction pipes and pipettes can be made of a rubber tube with 1 mm lumen and 2 mm walls. Pieces about 1 cm long are cut off this tube. These pieces are placed on the point of a glass rod (e. g. a spatula), the lower edge being ground obliquely to fit the bottom of the glass cup.

to have a lamp placed at some distance behind the extraction chamber.

The levelling bulb, which may be placed in an upper or a lower metal ring, is connected with the rest of the apparatus by means of a thick-walled rubber tube, about 170 cm long (of so-called vacuum quality). When the apparatus is in use both the levelling bulb, the rubber tube, and the manometer tube are filled with mercury. The flow of mercury from the levelling bulb to the apparatus is regulated by means of a cock, C, while another cock (B) serves to remove the small amounts of gas which, while the apparatus is left to stand, diffuse through the rubber tube. Adhesive plaster and thin copper wire are wound round the ends of the tube to prevent it from slipping off.

Mounting of the apparatus. When the apparatus is supplied by the dealer the extraction chamber is as a rule not mounted on it. It is mounted by means of a special rubber tube, 3.5 cm in diameter and with walls 1.5 cm thick. Before use the rubber tube is boiled for 5 minutes in dilute sodium hydroxide solution (0.5 n), after which it is washed with water. Then it is boiled for 5 minutes in dilute hydrochloric acid (1 part of concentrated hydrochloric acid to 25 parts of water) and again washed thoroughly with water. Before mounting the inner side of the rubber tube is covered with a thin layer of cock lubricant by means of a spatula. The rubber tube is then placed on the right, vertical glass tube of the apparatus, and the extraction chamber is fixed, care being taken that there is a space of 2—3 millimetres between the ends of the two glass tubes (see Fig. 19). The distance to the lower glass tube may be measured before the placing of the chamber, by means of a spatula introduced into the lumen of the tube.

The filling of the water jacket with distilled water takes place after removal of the thermometer inserted in the upper rubber

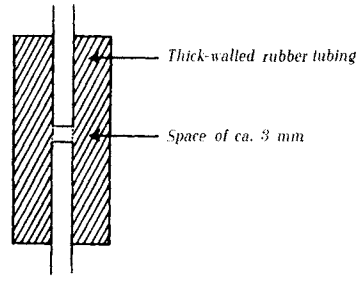

Fig. 19. Drawing of rubber connection between the extraction chamber and the apparatus.

stopper. In order to prevent the growth of bacteria and fungi it may be recommended to dissolve a little methylparaoxybenzoate in the water.

*Estimation of the Quality of the Extraction Chamber.**)

It is of importance for the convenient performance of the analyses that the top of the chamber has the proper shape (see Fig. 20), since otherwise a gas bubble will easily be caught below the cock. Apparatus with this flaw should not be accepted. Before purchasing the extraction chamber it may be recommended to make the two following tests on the unmounted chamber for the estimation of the drainage from the upper part of the chamber and the shape of the cup respectively.

In *testing for the correct drainage* from the top of the chamber a little water is poured into the cup, of which a couple of c. c. are admitted to the chamber by opening cock A. Then a couple of c. c. of mercury are poured into the cup and it is now observed by opening and closing cock A whether the mercury flowing through the bore of the cock is able quickly to remove the water from the upper part of the chamber under the cock. If this is not possible after a couple of trials, the chamber should not be accepted.

In *testing the shape of the cup* a little methylene blue solution is placed in the cup and is then by opening cock A admitted to the chamber. After this the cup should be empty. In not a few cases a coloured ring is seen at the bottom of the cup, indicating a wrong shape of the bottom (see Fig. 20).

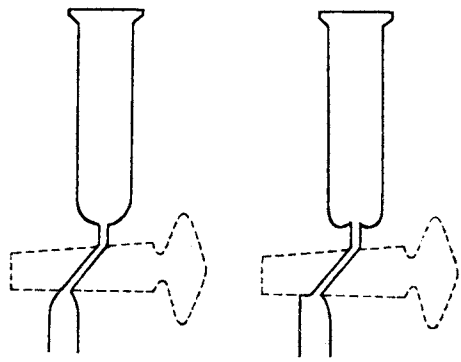

Fig. 20.
Correct shape. Incorrect shape.
Drawing of cup and top of the extraction chamber.

*) Of Danish made apparatus and extraction chambers the author may recommend those manufactured by the firm of F. C. Jacob, Hauserplads, Copenhagen.

Simple Method for the Calibration of the Extraction Chamber.

The carefully cleaned chamber is placed top end downwards in a metal holder. Cock A is closed and purified mercury is admitted with a pipette or a burette, until the top of the mercury meniscus is on a level with the gradation mark concerned (with a normal position of the chamber this will correspond to the concave water meniscus). The finer adjustment of the mercury to the mark can be carried out by means of cock A by ejection of mercury through the curved capillary outlet. After adjustment of the meniscus the mercury is emptied through the cup into a weighing bottle by opening cock A. From the weight found the volume of the mercury at the temperature in question is calculated.

If the gradation deviates from the volume indicated, correction must be made for the deviation by calculation of the analytical results. If thus the volume found is 2.06 c. c. instead of 2.00 c. c, the factors in the first column of Table 12 should be multiplied by 1.03.

Filling of the apparatus with mercury.

The apparatus is filled with mercury from the levelling bulb. The flow is regulated by means of cock C. By opening and closing the other cocks the gas is expelled from the chamber and the manometer tube. About 200 c. c. of mercury are used to fill the apparatus. The filling ceases when the levelling bulb, after the chamber and the manometer tube have been filled, is about half full of mercury, when it is placed in the upper ring. After filling, the chamber is evacuated in order to remove the gas adhering to the mercury and the walls of the chamber.

Lubricating and securing the cocks. The cocks are carefully cleaned with a cloth moistened in ether and then lubricated with cock lubricant.*) After lubrication the cocks are secured by means of a thin copper wire or a piece of string.

For the lubrication of cock A the following special method is used. The extraction chamber is half filled with water, after which the cock is removed. After the lubricated cock

*) Cock lubricant is made as follows. 1 part of pure, non-vulcanised rubber (e. g. a rubber glove) is cut into small pieces, preferably a couple of mm in size. The pieces are heated with 4 parts of vaseline and 1 part of paraffin in an oven at 110° with occasional stirring until the rubber has been dissolved and the mass is of a uniform appearance, which takes c. 2 days. Then the mixture is heated with a micro-burner for ½ hour at 150°—160° and filtered through gauze to remove undissolved particles.

has been inserted any grease adhering to the bores of the cock is removed by absorption of the water from the chamber, the first part of the water being drawn off through the cup, the last part through the curved capillary tube by fitting the rubber tube from the suction pump directly on the capillary tube.

The lubrication of cock C is carried out in the following way. All fluid is drawn off the chamber through the cup. Then cock A is closed leaving the extraction chamber filled with mercury. The levelling bulb is then fastened by a loop of string to the lower metal ring in such a position that the surface of the mercury in the bulb is lower than cock C. When cock B is opened the mercury will sink below cock C which can now be removed without difficulty.

Removal of water vapour from the manometer tube. After the apparatus has been filled with mercury, one or two drops of trimethyleneglycol are admitted into the manometer tube through the upper cock (D) to remove the moisture which as the mercury flows back and forth is transferred during the analysis from the chamber to the manometer tube. Then the bore of cock D is closed with mercury. During the introduction of the trimethyleneglycol care must be taken that no air is admitted to the manometer.*) The absence of water (and air) in the manometer tube is controlled by drawing off the fluid from the extraction chamber so that the latter is filled with mercury, and after closing cock A lowering the mercury to the 2 c. c. mark. The difference between the mercury surface in the chamber and in the manometer, which is most easily measured by placing a ruler from the mercury surface in the chamber at right angles to the manometer tube, will then correspond to the pressure of the water vapour at the temperature in question. The water vapour in the chamber is derived from the delicate film of fluid which will always remain after the withdrawal of fluid. The pressure of water vapour at various temperatures will appear from Table 11. The trimethyleneglycol is renewed at intervals of a couple of months.

*) Even in the complete absence of gas in the manometer tube the mercury in the tube with the levelling bulb at rest in the lower ring will not reach cock D, there being a vacuum between the mercury and the cock.

Table 11.

Pressure of Water Vapour at various Temperatures.

Temperature C°	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Pressure mm Hg	13	14	14	15	16	17	19	20	21	22	24	25	27	28	30	32

Small amounts of mercury for closing the bores of cock A during the extractions are poured from a small bottle closed with a pierced cork stopper.

Cleaning of the mercury collected in the suction bottle can take place by filtration or distillation. The mercury may be passed repeatedly through ordinary filter paper placed in a glass funnel and provided with a hole a couple of millimetres in diameter corresponding to the point of the filter.

Cleaning of the extraction chamber. After it has been used for some time it may be desirable to clean the chamber thoroughly. This can be done by filling the whole chamber with chromic sulphuric acid*) which may, if necessary, be left in the chamber over night. After filling with this cleansing solution the levelling bulb must not be lowered under the level of the lower metal ring as otherwise the rubber connection between the chamber and the apparatus may be damaged.

When the apparatus is not in use both the chamber and the cup are filled with water, cocks A and C are open, and the levelling bulb is placed in the lower ring. Before the use of the apparatus the water is drawn off with the suction tube.

The whole apparatus should only be cleaned if water has got into the manometer tube, or if so much dirty cock lubricant has been deposited in it that it is difficult to take the readings. Before cleaning the apparatus is emptied of mercury, after which the levelling bulb and rubber tube are removed. The rubber tube of the vacuum pump is now connected directly with the glass tube under cock C and the apparatus is cleaned and dried by applying strong suction and drawing water, chromic sulphuric acid, water, acetone, and air through it.

*) Chromic sulphuric acid: Crystallised sodium dichromate 10 g. Distilled water 10 c. c. Raw sulphuric acid up to 200 g.

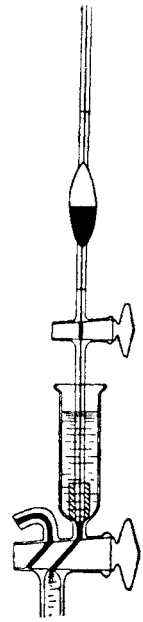

Fig. 21. Introduction of sample into the chamber by means of an Ostwald-Van Slyke pipette, provided with a rubber ring. After Van Slyke.

Introduction of samples into the chamber.

In the original method of bicarbonate determination according to Van Slyke and Neill samples were introduced into the chamber by means of an Ostwald pipette with a ground glass cock (see Fig. 21). The point of the pipette is provided with a rubber ring which allows of a firm contact with the bottom of the glass cup (see the foot note p. 185). In the simplified method, which will also be described in this guide an ordinary pipette without a rubber ring is used.

Testing for airtightness. 2—3 c. c. of water are measured into the beaker and introduced into the chamber through cock A, without admitting any air. The bore in cock A is closed with mercury, and the gas is extracted from the water by lowering the mercury to the 50 c. c. mark and afterwards shaking it for 2 minutes. After reading the pressure at the 0.5 c. c. mark the mercury is again lowered to the 50 c. c. mark and the shaking is repeated for one minute, whereupon the pressure is again read at the 0.5 c. c. mark. If the apparatus is not tight the pressure will have risen between the

two readings. In order to secure tightness during the extraction it is absolutely necessary to have both the bores of cock A filled with mercury.

As ordinary *measures of precaution* it should be stated that the levelling bulb must never be lowered beneath the level of the lower ring unless cock A is closed, as in the opposite case gas and fluid will be drawn from the chamber into the manometer tube. Care should also be taken not to shake the chamber when it is filled with mercury as the glass will then easily break.

2. Macro-method for the Determination of the Bicarbonate Content of the Plasma or the Serum according to Van Slyke and Neill.[221]

The principle of the analysis is stated on p. 13 where it is pointed out that the determination, in addition to the amount of carbon dioxide fixed as bicarbonate, also comprises the small amount of physically absorbed carbon dioxide that is present. In practice no great error will be committed by regarding the whole as bicarbonate.

Taking of blood samples. Blood samples for bicarbonate analysis are collected under paraffin oil in order to avoid loss of carbon dioxide to the air. It is easiest to take the sample from a cubital vein by means of a syringe containing some few c. c. of paraffin oil. Prolonged stasis should be avoided. For duplicate analyses about 6 c. c. of blood will be sufficent. The blood is transferred to a centrifuge tube about 15 c.c. in size, containing 1–2 c.c. of paraffin oil. Contact with the air is avoided by taking care that during the transfer the point of the needle is always held under the surface of the oil. In serum analyses the glass is put aside for coagulation. If it is desired to use plasma, coagulation is prevented by a little neutral potassium oxalate placed at the bottom of the centrifuge tube which after the introduction of the blood is carefully mixed with it by means of a pointed spatula. Before being pipetted off the sample is centrifuged for a couple of minutes.

Reagents: 1 n lactic acid*)
0.1 n lactic acid*)
Octylalcohol
5 n sodium hydroxide

Cleaning of the chamber before the analysis. Before each analysis the chamber is cleaned once with dilute lactic acid and once with water; about 4 c. c. of water and 1 c. c. of 1 n lactic acid are measured into the cup. The measurements are most easily made by means of the gradations of the cup and need not be accurate. The greater part of the contents of the cup is then introduced into the chamber by the opening of cock A without any air being admitted. Then the bore in cock A is closed with a couple of drops of mercury and the mercury in the chamber is lowered by means of the levelling bulb to the 50 c. c. mark, whereupon cock C is closed and the levelling bulb is placed in the lower ring. The lowering of the levelling bulb is done with the left hand, the opening and closing of the cocks with the right hand. During the lowering of the mercury to the 50 c. c. mark it is necessary to lower the levelling bulb almost to the floor. The chamber is then shaken for about 20 seconds. After the shaking, cock C is opened and as a result of the vacuum the fluid will rise into the upper part of the chamber. The suction tube is now with the left hand placed firmly against the bottom of the cup, cock A is opened, and the washing water is drawn off.

After it has been cleaned with dilute lactic acid, the chamber is washed in a similar way with 4—5 c. c. of water.

Analytical technique.

Introduction of the sample and the reagent into the chamber.

At the beginning of the analysis the chamber, after the washing water has been drawn off, is filled with mercury. With a medicine dropper one drop of octylalcohol is placed in the cup after which the drop is admitted to the capillary tube under the cup, without air getting in, by cautious opening of cock A. After the introduction cocks A and C are closed. Then 2.5 c. c. of 0.1 n lactic acid are measured into the cup. The measurement can be made with sufficient exactness by means of the gradations of the cup (excess lactic acid, if

*) In order to prevent the growth of fungi in the lactic acid solutions methylparaoxybenzoate in a 0.05—0.1 p. c. concentration may be added to them.

any, is removed from the cup by suction). The sample of the plasma is then drawn off in a 1 c. c. Ostwald pipette, the point of which is carefully wiped. It is important to make sure that no small drops of paraffin oil are drawn into the pipette with the sample. The Ostwald pipette is then with the left hand pressed firmly against the bottom of the beaker, while at the same time the pipette must be kept in a vertical position (see Fig. 21). To introduce the plasma sample into the chamber the pipette cock, cock A, and cock C are now opened in succession. At the opening of the pipette cock there will be no flow from the pipette if the latter is held in the correct position with the rubber ring pressed firmly against the bottom of the cup. On the other hand, the plasma sample will often rise a little into the pipette so that the surface of the plasma will be raised a little above the uppermost mark of the pipette. Without taking this into account the plasma sample is to be measured off right down to the lowermost mark on the pipette. Cock A is opened cautiously so that the emptying of the pipette may take place at a suitable rate. At the succeeding opening of cock C the last part of the sample is finally evacuated (to the lowermost mark on the pipette). The finer regulation of the outflow can more easily be done with cock C than with cock A. After the sample has been measured off, the cocks are closed in the reverse order (cock C, cock A, and the pipette cock), whereupon the pipette is removed. The lactic acid is now admitted from the cup to the chamber by opening cock A and regulating the inflow with cock C. No air must enter the chamber during the introduction. When the surface of the lactic acid solution has just reached the bottom of the cup, cock A is closed, whereupon cock C is opened. About 1 c. c. of water is placed in the cup and the bore in cock A is closed with mercury. The water in the cup serves to prevent the admission of air into the chamber while the bore of the cock is being closed. After it has been closed, the water together with the excess mercury is removed by suction.

Extraction of carbon dioxide.
Measurement of the extracted amount of carbon dioxide.

After cock A has been closed the mercury in the chamber is lowered by means of the levelling bulb until the surface of the mercury is on a level with the 50 c. c. mark, after which cock C is closed and the levelling bulb is placed in

the lower ring. The chamber is then shaken for 2 minutes.

The extracted amount of carbon dioxide is measured by adjusting the surface of the fluid to the 2 c. c. mark. During the adjustment the levelling bulb is placed in the lower ring, and the lamp behind the chamber is alight. The adjustment is achieved by cautious opening of cock C, the fluid rising into the chamber as a result of the vacuum. After exact adjustment of the meniscus the pressure (p 1) is read from the manometer, and the temperature noted.

If during the adjustment the 2 c. c. mark is passed, it is necessary to lower the mercury again to the 50 c. c. mark and repeat the shaking for 1 minute, as otherwise the values will be too low owing to reabsorption of carbon dioxide.

After the reading of p 1, cock C is opened, and the fluid will rise still higher in the chamber. About 1 c. c. of 5 n sodium hydroxide is placed in the cup; of this 0.2 c. c. is introduced into the chamber by the slow opening of cock A. The bore of the cock is closed with mercury, and the levelling bulb is lowered until the surface of the fluid is just under the 2 c. c. mark, whereupon cock C is closed and the levelling bulb is placed in the lower ring. The lowering is done slowly so that the fluid may be drained completely from the wall of the upper part of the chamber. Care should be taken that no fluid is left at the top of the chamber just below the cock. If this is the case the fluid is removed by admitting a little mercury from the cup into the chamber. After 20 seconds the absorption of carbon dioxide is complete. The meniscus is again, by regulation with cock C, brought up to the 2 c. c. mark and the pressure (p 2) is read.

The fluid is then drawn off as described under the cleaning of the chamber.

Blank value.

The blank value (c) is determined by performing the analysis with 1 c. c. of water instead of plasma. The blank value is about 1 mm. It is sufficient to determine the value in connection with the renewal of the reagents.

Calculation.

Millimols of bicarbonate per litre of plasma or serum = (p 1 — p 2 — c) factor. The factors are given in Table 12, p. 200.

Simplified Technique for the Introduction of the Plasma Sample into the Chamber by means of an ordinary Pipette.

The following technique, which does not require the use of an Ostwald pipette, is fully applicable for clinical purposes.

After admitting one drop of octylalcohol into the bore of the cock 2.5 c. c. of 0.1 n lactic acid are measured into the cup. 1 c. c. of plasma is then drawn off in an ordinary pipette, the point of which is placed under the surface of the lactic acid. The plasma sample is then cautiously allowed to flow out of the pipette and the sample will settle at the bottom of the cup under the lactic acid solution. The last drops of the plasma are removed from the pipette by the following manipulations. The pipette is lifted carefully until the point is just under the surface of the lactic acid. Then the upper opening of the pipette is closed with the right index finger and the left palm is closed firmly round the expanded part of the pipette. Because of the warmth of the hand the air in the pipette is heated so much that the last drops are expelled from the point of the pipette. By cautious opening of cocks A and C the sample and the lactic acid are then introduced into the chamber without any air getting in.

The rest of the analysis is carried out as described above.

3. Micro-method for the Determination of the Bicarbonate Content of Serum or Plasma according to Van Slyke and Neill.[221]

Taking of blood samples.

For the anaerobic taking of blood samples from the heel or the ear for micro-analysis the following simple technique is recommended (Kirk).[97] A micro test tube about 11 by 50 mm*) is filled to the brim with paraffin oil and placed in a small beaker. Then sterile vaseline is applied to the skin at the place of incision in the heel or the ear, and after incision with a sharp cataract knife the surface of the oil in the micro test tube is brought into direct contact with the skin. In this

*) If the diameter of the tube is very much smaller the flow of the blood drops into the tube and the outflow of the paraffin oil will be rendered difficult.

way the paraffin oil will be drawn towards the skin so that the outflowing drops of blood are not at any time brought into contact with the air. On taking blood from the ear stasis is easily produced by placing a clamp at the place of the attachment of the ear lobe. With this procedure it is generally possible in the course of ½—1 minute to collect sufficient blood for analysis. The paraffin oil displaced from the tube during the taking of the sample is collected in the beaker so that dirtying with oil is avoided. The micro test tube is then placed in a centrifuge tube (with cotton wool at the bottom) and is centrifuged for 2 minutes with about 2500 revolutions per minute. It is often possible, especially in the cases where ½—1 hour has elapsed since the taking of the samples, already after the first centrifuging to obtain a clear separation of the serum and the blood coagulum. If the serum is not sufficiently separated after the centrifugation the blood coagulum is pressed together with a thin wooden stick after which the centrifuging is repeated. Before the sample is pipetted off, the paraffin above it is cautiously drawn off, until only a layer of oil a few millimetres thick is left over the serum.

Reagents: 1 n lactic acid*)
. 0.01 n lactic acid*)
Octylalcohol
5 n sodium hydroxide

Cleaning of the chamber prior to the analysis is carried out as described under the macro-analysis.

Analytical technique.

Introduction of octylalcohol and 0.01 n lactic acid into the chamber.

At the beginning of the analysis the chamber, after the washing water has been drawn off, is filled with mercury With a medicine dropper one drop of octylalcohol is admitted to the cup of the chamber, after which, by cautious opening of cock A, the drop is introduced into the capillary tube under the cup without any air getting in. Cocks A and C are then closed. After this 3 c.c. of 0.01 n lactic acid are measured into the cup. The measurement may be made with

*) See footnote p. 193.

sufficient accuracy by means of the gradations of the cup. The lactic acid is then introduced into the chamber from the cup by opening cock A and regulating the inflow with cock C. No air must be admitted to the chamber during this proceeding. When the surface of the lactic acid solution has just reached the bottom of the cup, cock A is closed, after which cock C is opened. About 1 c.c. of water is placed in the cup and the bore of cock A is closed with mercury. The water in the cup serves to prevent the admission of air into the chamber during the closing of the bore in the cock. After the closing the water and excess mercury are removed by suction.

Extraction and Removal of the Gas physically absorbed in the Lactic Acid Solution.

After cock A has been closed the mercury in the chamber is lowered by means of the levelling bulb until the surface is on a level with the 50 c.c. mark, cock C being then closed and the levelling bulb placed in the lower ring. The chamber is then shaken for 2 minutes. After the shaking the extracted amount of gas is definitively removed and the greater part of the lactic acid solution temporarily removed from the chamber by the following manipulations:

1. Cock C is opened and owing to the vacuum the fluid will rise into the upper part of the chamber.
2. The levelling bulb is placed in the upper ring.
3. Cock C is closed.
4. Cock A is opened.
5. Cock C is slowly opened whereby the gas and the fluid are expelled through the bore in cock A. The expulsion is continued until there is only 0.5 c.c. of fluid left in the chamber, (i.e. until the mercury surface is on a level with the 0.5 c.c. mark) after which cock C is closed.

Introduction of the Serum Sample into the Chamber.

The serum sample is drawn into a 0.1 or 0.2 c.c. pipette. After measurement of the sample the point of the pipette is placed against the bottom of the cup, the index finger of the right hand being pressed against the upper opening of the pipette and the contents thus prevented from running out. By cautious opening of cock C with the left hand the lactic acid solution is made to flow from the cup into the chamber. At the same time the finger is removed from the opening of the pipette, and the contents of the pipette will then flow

out of it and be carried with the lactic acid stream into the chamber. The inflow from the cup is continued until the surface of the mercury has reached the 2 c.c. mark, when cock C is closed. During the introduction of the serum sample air will often get into the chamber through the lumen of the pipette. This is removed from the chamber without loss of fluid by the following manipulations:

1. The levelling bulb is placed in the upper ring.
2. Cock C is slowly opened, whereby the air is expelled through the bore in cock A. The expulsion is continued until the last air buble has left the bore in the cock, after which cock C is closed.
3. The levelling bulb is placed in the lower ring.
4. Cock C is opened, whereby lactic acid solution is admitted from the cup to the chamber until the mercury surface is again on a level with the 2 c.c.mark.

Then cock C is closed, the bore in cock A is closed with mercury, and excess lactic acid and mercury removed from the cup by suction.

Extraction of Carbon Dioxide and Measurement of the extracted Amount of Carbon Dioxide.

After cock A has been closed, cock C is opened and by means of the levelling bulb the mercury in the chamber is lowered to the 50 c.c. mark, cock C is closed and the levelling bulb placed in the lower ring. The chamber is then shaken for 2 minutes.

The extracted amount of carbon dioxide is measured by adjusting the surface of the fluid to the 0.5 c.c. mark. During the adjustment the levelling bulb is placed in the lower ring, and the lamp behind the chamber is alight. The adjustment takes place by a cautious opening of cock C, and owing to the vacuum the fluid will then rise into the chamber. After accurate adjustment of the meniscus the pressure (p 1) is read on the manometer and the temperature noted. If the 0.5 c.c. mark is passed during the adjustment it will be necessary to lower the mercury to the 50 c.c. mark again and repeat the shaking for 1 minute, as otherwise the values obtained will be too low, owing to the reabsorption of carbon dioxide.

After the p 1 reading has been taken cock C is opened and the fluid will rise still higher in the chamber. 0.2 c.c. of 5 n sodium hydroxide is then measured into the cup with a pipette and slowly introduced into the chamber by cautious

opening of cock A without admitting any air. The bore of the cock is then closed with mercury, and the levelling bulb is lowered until the surface of the fluid is just under the 0.5 c.c. mark, after which cock C is closed, and the levelling bulb is placed in the lower ring. The lowering is done slowly so that the fluid may be completely drained from the wall of the upper part of the chamber. Care must be taken that no fluid remains at the top of the chamber just below the cock. If this should be the case, the fluid is removed by admitting a little mercury from the cup to the chamber. After 20 seconds the absorption of the carbon dioxide is complete. The meniscus is again by regulation with cock C brought up to the 0.5 c.c. mark, and the pressure (p 2) is read. The fluid is then removed by suction as described under the cleaning of the chamber.

Blank value.

Determination of the blank value (c) is made by performing the analysis with 0.1 or 0.2 c.c. of water instead of serum. The blank value is about 6—8 mm. It is sufficient to determine the value in connection with the renewal of the reagents.

Table 12.

Factors for the Calculation of the Bicarbonate Content of Plasma or Serum, in Millimols per Litre.

Temperature C	Macro-method 1 c.c. sample	Micro-method 0.2 c.c. sample	Micro-method 0.1 c.c. sample
15	0.1229	0.1514	0.3028
16	0.1222	0.1507	0.3014
17	0.1215	0.1499	0.2998
18	0.1208	0.1492	0.2984
19	0.1202	0.1486	0.2972
20	0.1196	0.1479	0.2958
21	0.1190	0.1472	0.2944
22	0.1183	0.1466	0.2932
23	0.1177	0.1459	0.2918
24	0.1171	0.1453	0.2906
25	0.1165	0.1446	0.2892
26	0.1160	0.1440	0.2880
27	0.1154	0.1434	0.2868
28	0.1149	0.1428	0.2856
29	0.1143	0.1422	0.2844
30	0.1138	0.1416	0.2832

Calculation.

Millimols of bicarbonate per litre of serum = (p 1 — p 2 — c) factor.

The factors are given in Table 12, p. 200.

Sending of blood samples for macro- or micro-determination of serum bicarbonate. On sending anaerobically collected blood samples the following technique may be recommended. With a pipette or by means of a suction pump the paraffin oil is carefully drawn off until only a layer about 1 mm thick remains over the blood sample. A small piece of solid paraffin is then melted in a porcelain dish and poured into the glass in the fluid condition, where it will shortly after become solid and form an air-tight seal.

When the sample is to be used a heated nail, (or better still, one of the metal cylinders designed for piercing corks) is passed into the paraffin layer. This will make a hole in the paraffin plug large enough to allow of the insertion of a pipette.

Index of Case Records.

(The figures in parenthesis denote the number of the page)

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