ACETONAEMIA IN CHILDREN.
Introduction.

The term Acetonaemia is used in this thesis to denote those changes in the blood and urine which occur in the condition of Acid Intoxication, as well as the clinical manifestations. These changes are brought about by the presence of acetone bodies, viz: aceto-acetic acid, B-oxybutyric acid and Acetone. For this purpose the term "acidosis" may be defined as a reduction of the plasma bicarbonate. Such reduction may or may not be due to, or associated with, an excess of ketone bodies in the blood; that is to say, a condition of acidosis may be present and frequently is, without acetonaemia etc. As a matter of fact it has long been known that ketosis may occur in the presence of an alkalosis.

Ketosis is, of course, more commonly met with in children than in adults, because, in the former, owing to their comparatively poorly developed cerebral inhibition, with consequent lack of emotional control, greater and more frequent calls are made on the glycogen stores of the liver. It is for this reason too, I think, that the symptoms described in this article are more marked in nervous children, but they are certainly not confined to them. The one biochemical finding which is present in all these children is a lowered plasma
bicarbonate, though the diminution may only be slight. Until our knowledge of the subject of the condition is more complete, the term "the acid child" would be correct and convenient, and would best describe the patient.

The development of this subject has been very gradual, although it has occupied a prominent place in the field of medicine for several decades. Numerous erroneous conceptions have arisen from time to time, and these are being eliminated only with difficulty. In recent years there has been renewed activity in the study of acidosis, particularly in those types of non-diabetic origin.

It had long been known that diabetic acid appeared in the urine, and acetone in the breath, of a diabetic patient who was progressing unfavourably. But it is not recognised, that these symptoms appear in many other conditions such as hyperemesis gravidarum, cyclical vomiting, after anaesthetics etc. We must consider what general significance is to be attached to a train of symptoms occurring under conditions apparently so diverse.

It will suffice at this stage to give a brief clinical picture of the condition of recurrent vomiting in children.

The attacks occur in children between the ages of 3 years and 11 years. The frequency of the attacks of vomiting is very variable, a common interval being 3 months, but may occur even weekly.

There may be a prodromal period in which
dyspnoea, sighing respirations, offensive breath, choreic movements, and general restlessness have been noted. Lassitude, drowsiness, headache, pyrexia, vomiting, and marked muscular weakness are the almost constant symptoms. Abdominal pain is frequently complained of, even before vomiting sets in, and constipation is generally present, though diarrhoea accompanies the vomiting in some cases. Pyrexia is invariably present at the outset, and often reaches 103° F on the first day. The muscular prostration may be extreme with transient squints, loss of knee jerks, and carination of the abdomen. In such a case drowsiness may give place to actual coma, and not infrequently there is a mild jaundice with pale coloured stools. The urine is as a rule acid, scanty, high-coloured, and contains an excess of acetone bodies. The vomiting is persistent and is brought on by the mere sight of food — even water is rejected. The vomited matter is usually acid, and is often highly coloured with bile especially towards the end of the attack. The attacks usually last two or three days and then gradually and spontaneously remit, leaving the child after a few days in normal health.

Attacks continue at regular or irregular intervals till 12 or 13 years of age, when they tend to become less frequent and less severe, and by the time of puberty they have generally ceased altogether. Sometimes at puberty the attacks are
replaced by symptoms of migraine. In some cases cyclical vomiting commences in infancy, though usually in an atypical form. It is now well frequently recognised that cyclical vomiting occurs more in children with an inherited or acquired nervous instability.

A review of the literature at this time is extensive, but a much clearer conception of a rather complex condition has been the result of recent investigation. It is not so long since a great many diseases were vaguely thought to be due to acids in the system, but there has been a gradual development of more scientific theories of the nature of acidosis.

Many workers starting with Miquel in 1851, had given strong mineral acids to animals, and observed an increase in the bases excreted.

We now know clearly since the work of Walters and others, that acids, as such, experimentally used are capable of producing a peculiar train of symptoms when ingested in large amounts. From the early work of Walters, it was made plain that, in considering the action of acids on the body, the character of the acid must be taken into account as well as the strength injected. He showed that double the fatal dose of acid could be given in these experiments, without any symptoms of poisoning at all, if a solution of sodium bicarbonate was injected subcutaneously, after the acid was administered.
Mention should also be made of the great work of Stadelmaier and the attention he drew to the similarity of the symptom complex of diabetic coma, to that of acid intoxication (as it is known from the work of Walters) and definitely adopts acid intoxication as the cause of diabetic coma.

In the present thesis, it is proposed to deal with the recent developments in connection with the subject of acidosis and with the suitable treatment of these cases, particularly in children.

It is an effort to determine the nature of these recurring waves of disturbed metabolism in children, which account for the peculiar instability both of physical health and of conduct, characteristic of the nervous child, and which are manifested in the "bouts" or "turns" of which, in one form or another, complaint is always made.

The investigations which have been carried out, and the records which have been made, are taken from cases occurring in general practice. A mild degree of acidosis is common among children and causes real distress, but these cases may never reach hospital. Other types of acidosis have been examined for comparison and have been studied in hospital.

It is only by examination of the general condition of the child during the quiescent period, that local foci of infection can be removed, also prodromal symptoms can be recognised, and the condition aborted by treatment.
Historical Outline.

The theory of acidosis had its inception in 1850, when Boussingault made the extremely valuable discovery, that large amounts of ammonia frequently appear in the urine of diabetic patients.

Many workers have investigated this question of acidosis, and probably the simplest form of acid poisoning is that induced by the experimental administration of mineral acids.

Miquel, as far back as 1851 had given strong mineral acids to animals, and observed an increase in the amount of bases, excreted in the urine.

Jaquet also found that the effects of mineral acid poisoning were much less marked in dogs than in rabbits. (He demonstrated in a striking manner that the alkalinity of the blood was little affected, by the introduction of relatively large amounts of acid. For instance, after the injection of enough Hydrochloric acid into a vein to neutralise all the blood, its alkalinity was only reduced by 4% - 7%, a reduction less than the mere dilution with fluid would cause.)

Petters in 1857 recorded the results of his investigations into the cause of the curious fruity odours of the breath and urine, found in some cases of diabetes mellitus, and showed that this odour was due to the presence of acetone.

In 1860 Kaulick showed that acetone may appear in the urine in a variety of other conditions such as Typhoid Fever, profuse diarrhoea, and vomiting,
severe wasting etc. and put forward the view that this acetone is produced by intestinal fermentation, and the source is the carbohydrate of the dietary.

In 1865 Cantani further extended the list of conditions under which acetonaemia may appear, and brought forward evidence to show that acetone was formed by the liver, and that the exciting cause was starvation.

Kussmaul's classical work on diabetes and diabetic coma with its attendant symptoms, appeared in 1874. He considered that the cause of coma and its symptoms was to be found in the presence of an acetonaemia.

Walters in 1877 produced a "comatose" state in rabbits by injecting mineral and organic acids. He pointed out that the carnivora have a greater power of resistance to acids, as their food consists of acid producing material, and contains comparatively little base. Dogs have the power of producing NH3, with which they neutralise the acid to a large extent. Walters gave twice as much acid to dogs as to rabbits with much less effect.

The alkalinity of the blood in these experiments was reduced, though not abolished - that is to say, death occurs before the blood can become acid to litmus. Walters also showed that these symptoms of fatal effects could be obviated by introducing alkali into the body. Double the fatal dose could be given without symptoms, if a solution of sodium bicarbonate is injected subcutaneously.
after the acid is administered.

It has been supposed that in acidosis the blood can no longer carry carbon dioxide from the tissues to the lungs, because its soda is taken into combination with the acid administered. However there is some experimental evidence against this explanation, e.g. if alkalies are administered the symptoms are obviated.

Jaquet also remarked on this fact, and found that the alkalinity of the blood was but little affected by the introduction of relatively large amounts of acid. He observes, that after an intravenous injection of a quantity of Hydrochloric acid, sufficient to neutralize all the blood, the alkalinity was only reduced by 4% - 7%.

In 1880 Coranda and Hallervordon furthered the discovery of hydroxybutyric acid. The latter points out that the high NH₃ excretion in diabetes must be sought in a high excretion of acid. He also goes so far as to say that not only inorganic acids but also lactic, glycuronic acids etc. may unite with the ammonia and add to its excretion. In one of his patients to whom large doses of sodium bicarbonate were given, no appreciable effect on the excretion of ammonia was noted.

In the same year Gaethje published a paper. He made careful experiments on the administration of H₂SO₄ to a dog. His results showed, that when
sufficient acid was given to increase the acid excreted by more than 3 times the normal, there was nevertheless sufficient base excreted to neutralise the acid, but very little of the extra acid was neutralised by the fixed bases, almost all of it being neutralized by ammonia.

In 1883 Stadelmaier from his observations, concluded that in a diabetic urine which is strongly acid and contains ammonia, there must be some unknown acid in considerable quantity. From chemical analysis this acid is crotonic, but this he said had no relation to aceto-acetic acid. Stadelmaier drew attention to the similarity of the symptoms of diabetic coma to those of acid intoxication, (as it was known from the work of Walters) and definitely adopts acid intoxication as the cause of coma.

Knelz and Minkowski in 1884 proved that the organic acid found in the acid intoxication of diabetes, was laevo-rotatory B-oxybutyric acid. When a positive ferric chloride reaction was obtained, the urine which gave the reaction always contained B-oxybutyric acid, and Knelz found the acid on several occasions when this chemical reaction was negative. In one of his cases he estimates the amount of acid excreted in 24 hours, by determining the rotation of the fermented urine, and assuming that the specific rotation of the acid is only one third that of glucose, in this way he arrives at 22.65 grams.
Minkowski, Stadelmaier, Magnus Levy and Von Noorden have all quoted this specific rotation of acid as correct.

The combined work of these researchers goes to prove (up to the year 1884) the presence of acetone and diacetic acid in the urine of diabetics, but they do not regard their presence as being toxic. Laevorotatory hydroxybutyric acid was, in 1884, discovered to be present in such urines in large amounts. Stadelmaier, Walters and Hallervorden adopted the theory of acid intoxication, and accordingly Hallervorden prescribed alkalies in such cases. Minkowski however proved the inadequacy of its use in cases of coma, (By acid intoxication is meant an increase in concentration of Hydrogen ions) and was the first to suggest that hydroxybutyric acid was derived from fats and from amino acids.

Wolfe in 1886 recognised a relationship between aceto-acetic acid and hydroxybutyric acid.

From 1899-1901 important contributions on the subject were given by Magnus Levy, who supports vigorously the theory of acid intoxication. In his papers he attempts three things:

1. To show that diabetic coma is an acid poisoning.
2. To show that the acid which affects the poisoning is hydroxybutyric acid, and aceto-acetic acid being a very variable quantity of little significance, in so far as it is present, it too acts only as an acid.
3. To trace the origin of hydroxybutyric acid and therefore of its supposed derivatives, aceto-acetic acid and acetone.

It is to Magnus Levy that the honour is due for being the first to prepare crystallized hydroxybutyric acid, and he it was who first determined correctly the specific rotation of the acid. From time to time however a different view has come to the foreground, viz: that the acid substances aceto-acetic acid and B-oxybutyric acid were in themselves poisonous and caused the condition.

Rosenfeld writing in 1895 states - "Fat has only an action on acetonemia, in so far as it influences the causal factor of acetonemia - the decomposition of protein".

Mohr and Loel in 1902 showed an exact parallel between the acetone body and the fat in the patient's food, and also they demonstrated that butyric acid was derived directly from oxybutyric acid.

Scurvy-Rolfe in 1877 said that scurvy was due to acid poisoning, this view being recently supported by Sir Almroth Wright. They mention that the alkalinity of the blood is raised after administration of sodium citrate, but the experiments of Axelt Holst tend to modify their statement. He quotes a case of adult scurvy where the patient had lived for six months on rye, bread wheat and water.
The alkalinity of her blood remained normal. Sodium bicarbonate in this case did not afford relief.

**Recurrent vomiting in Children.** In 1882 many cases of recurrent vomiting in children were recorded, the origin of which was then unknown. Later observers noted the presence of acetone in the breath and vomit.

Batty Shaw & Tribe reported on 35 cases.
Chemical Considerations.

It is well known that certain food stuffs, particularly carbohydrates, and to a lesser degree glycerine, and organic acids, and amino acids, are potent in preventing the appearance of acetone as an end product of metabolism in the urine. In the absence of carbohydrates from a diet, or in the total absence of food, acetone will appear in the urine in 24 hours. In direct distinction to the carbohydrates, the fats of the food tend to increase the amount of acetone bodies in the urine.

When substances appear in the urine which are normally not there, it is possible that some pathological change has occurred, or that metabolism is imperfect or incomplete. Thus, uric acid is a normal constituent of the urine, but in an imperfect metabolism it becomes increased to pathological amounts.

The maintenance of a proper reaction of the blood, although a very simple matter in health, may even with extensive artificial aid become a difficult problem in disease. In disease, the body protects itself against an accumulation of acid, in fundamentally the same manner as it does in health. It responds not by the development of a new method for the disposal of acids, but by a quantitative increase in its normal processes.

The elimination of CO₂ is readily accomplished as long as fixed bases are available to permit
of its transportation to the lungs.

There is a certain reserve of fixed alkali which can be drawn upon to a limited extent without disturbing the body metabolism. This source of supply is not large and under certain conditions, especially diabetes, the bulk of the increased work falls upon the process of neutralisation by NH₃.

It has been shown by Embden and other workers that the liver has a double function. It produces the acetone bodies, but it also further destroys and converts them.

The Acetone bodies are:

(1) B-oxybutyric acid.
(2) Diacetic or aceto-acetic acid.
(3) Acetone.

B-oxybutyric acid is readily oxidised to diacetic acid, and this is converted into acetone by loss of CO₂. It is the quantitative estimation of these bodies in the urine, which gives the most accurate method of measuring the intensity of the acidosis. It is of little use to measure only the acetone that occurs in the urine, as much may be present in the form of diacetic acid.

Piper states "Experience has shown that there is no such thing as a urine containing only acetone". He found that all the urines examined when fresh, contained 70% or more of the acetone expressed as
aceto-acetic acid. Thus the nitroprusside test for acetone, and the ferric chloride test for diacetic acid, is applicable to show if these acids are present or not - but where a quantitative estimation of the total acetone is required, more elaborate methods must be sought.

Bainbridge says "Even in acidosis however, the alkalinity of the blood remains remarkably constant, though it may be temporarily disturbed by a large production of acid; and an abnormal alkalinity of the blood may co-exist, as Magnus Levy has shown, with a considerable degree of acidosis. And neither the total excretion of ammonia with urine, or the ammonia co-efficient (i.e. the proportion of the total nitrogen excreted as NH₃) necessarily or even usually corresponds to the degree of acidosis."

In the condition of acetonaemia in which the acetone bodies are present in the blood, coma is believed to result from the B-oxybutyric acid meeting with the sodium salts, which interferes with tissue respiration; the formation and excretion of ammonia is increased and assists in neutralising the acids. So long as the supply of alkali exists in sufficient quantity to neutralise the organic acids, so long will the alkalinity of the blood remain constant, and a condition of acid intoxication will not arise.

It is now generally accepted that acidosis is
essentially an impoverishment of the body in alkalies. It may be correctly defined as a
diminution in the reserve supply of fixed bases in
the blood, and other tissues of the body, the
physiochemical reaction of the blood remaining
unchanged except in very extreme conditions.

This "definition" should not be limited to the
carbonates, but should include the other fixed bases
of the body, likewise the changes should not be
limited to the blood but should include the other
tissues.

The significance of the excretion of the
acetone bodies in the urine has been much debated.
It was at one time thought they were derived from
glucose, because of their presence in diabetes.
Later they were attributed to proteins, but it is
now generally believed to be due to the abnormal
destruction of fats.

Recent investigations have served to emphasise,
that the fixed alkalies are necessary for the
physiological requirements of the body and that
they are essential to life.

With any ordinary mixed diet there is a
tendency towards a constant production of acid
radicals, but these radicals are prevented from
appearing as free acid in the blood or other tissues,
chiefly by two processes, namely excretion, and
neutralisation.

In an exactly similar manner, so the body also
provides against the accumulation of excessive amounts of alkali. It has been shown that the constancy of the reaction of the blood is even more carefully guarded than are the other great constants of the body, namely temperature and osmotic pressure.

Chemistry of Acetone Bodies.

**B-oxybutyric Acid.** \((\text{CH}_3\text{CHOHCH}_2\text{COOH})\)

This acid is the mother substance which in the acidosis caused by the acetone bodies, gives rise to diacetic acid (aceto-acetic acid) and acetone.

B-oxybutyric acid has not been found in healthy urine; in a normal person upon an ordinary diet a fair quantity of oxybutyric acid, when given by the mouth can be oxidised with ease, without the appearance of diacetic acid or acetone in the urine, but in diabetes this oxidation fails, as it does in animals deprived of the pancreas or poisoned with carbon monoxide or fed exclusively on fats. Its incomplete combustion under these conditions must be ascribed to a failure of some particular oxidation process, and not to a want of oxygen.

Since the acid can be dealt with by the healthy organism, and since the better oxidation by which it is formed, is one that can take place in the body, it is possible that it may be a normal intermediate product, and one of the usual links in the metabolic chain of transformations, for the major part hidden from us, along which the food materials pass to their final excretory products.
Oxybutyric acid is usually recognised in the urine by its laevo-rotatory power after any sugar present has been fermented. This method is not entirely satisfactory. When the acid is quantitatively estimated by a similar method, or by deducting the observed rotatory power of a diabetic urine, from that calculated from the amount of dextrose present, the results are not very reliable. The acid may be dissolved out from the urine in ether, and weighed, or its rotatory power determined. Probably the best method of estimation is that described by Ryffel in which the polarimeter is not used. This method gives accurate results with sodium oxybutyrate.

(b) Diacetic or aceto-acetic acid (\(CH_3CO,CH_2COOH\))

This acid appears in the urine when B-oxybutyric acid is injected, under the circumstances mentioned in the last section, though not in health. It may therefore be regarded as a derivative of B-oxybutyric acid and not as an independent product. When given by the mouth it is, in health, completely oxidised, probably by way of acetic acid; but in conditions of acidosis, it forms acetone.

In the laboratory it breaks up into acetone and carbon dioxide with ease, when heated or boiled with dilute acid or alkali.

The amount of diacetic acid in the urine may be roughly estimated by the depth of the claret colour produced in the ferric chloride test. Its quantitative estimation is usually made by
converting it into acetone, and estimating the acetone so formed, together with that preformed in the urine, as isoform, by the methods which are described.

Acetone \((\text{CH}_3\text{COCH}_3)\) 

Acetone occurs in the urine in the less severe cases of acidosis, in which the oxidation of oxybutyric and dicetic acids is complete. When given by the mouth it is not oxidised as easily as its precursors, and being a volatile substance is passed out by the lungs as well as by the kidneys. It is often found in small quantities in normal urine. Its characteristic sweet smell in the breath is often a means of diagnosis of diabetes, and of other forms of acidosis or acid intoxication. If more than half a gramme of acetone is present in the urine, dicetic acid is usually found, and if more than 1 gramme of acetone, oxybutyric acid as well. Any large amounts of acetone bodies consist mainly of B-oxybutyric acid.

The acetone bodies are found in the urine in a large number of clinical conditions, in which there is some degree of starvation involving the absence of carbohydrates. In diabetes, there is more or less inability to make use of the carbohydrates. The result in each case is that the individual is forced to supply his energy needs from protein and fat.
In looking therefore for the source of the acetone bodies attention has been directed to these food stuffs.

Tests for Clinical recognition of Acetone in urine.

1. Lieben's Iodoform Test.

The urine is best distilled although this is not absolutely necessary. 5 c.c. of the distillate are placed in a test tube. To this is added a few drops of KOH and a little Lugol's iodine solution. The mixture is warmed and if much acetone be present, an immediate precipitate of yellow iodoform crystals is observed. One can also detect the smell of iodoform. If only a small quantity of acetone be present (e.g. .0001 gm) the tube must be laid aside for some hours and the crystals allowed to separate out. The deposit may be examined under the microscope to detect the presence of the typical hexagonal plates of iodoform crystals.

2. Cunning's Iodoform Test.

Add Lugol's solution to the distillate and then enough ammonia to produce a dense black precipitate of nitrogen iodid. This precipitate will gradually disappear on standing, and when acetone is present, a yellow sediment consisting of iodoform will take its place. It can be recognised by its odour, or microscopically.

3. Lange's Nitroprusside test - also Legal's

A test tube is half filled with the suspected diluted urine and to this is added a few drops of glacial acetic acid. A freshly prepared solution of sodium nitroprusside is made up and a few drops are added to the urine. Ammonia is run on to the surface of this mixture. The presence of acetone gives an intense violet ring at the line of contact. This test is claimed to be more delicate than Legal's original one and the reaction has not the fallacy of being brought about by alcohol or aldehyde.

4. Rothera's Test for Acetone and aceto-acetic acid.

This reaction is by far the most satisfactory
test for ketosis. Saturate about 20 c.c. of urine with ammonium sulphate by shaking with the crystals in a test tube. Two or three drops of 10% ammonia, and a few drops of freshly prepared dilute solution of sodium nitroprusside in water, are added and shaken. If positive a delicate permanganate tinge develops, which gradually deepens. A brown colour does not constitute a positive reaction. The amount of aceto-acetic acid can be judged by the depth of colour and the rapidity with which it develops.

Tests for Aceto-Acetic Acid.

Urine must be tested shortly after it is voided. If this precaution is neglected, then the acid changes to acetone, and its presence is missed.

1. Gerhardt's Test (Diabetic ferric chloride Reaction)

Half fill a test tube with the suspected urine. Add drop by drop 10% ferric chloride solution and a deposit of iron phosphate will form, filter. To the filtrate add a few more drops of iron solution. If diacetic acid is present a dark reddish brown colour appears. The fluid in the tube is divided, one half boiled, and the other used as a control. If the reaction be due to diacetic acid, heating will decompose the acid and the colour will quickly diminish in intensity and ultimately disappear. The same will happen if the tube stands for some hours.

Fallacies Patients taking drugs such as salicylic acid, salol, aspirin, phenacetin, etc. will give the same Bordeaux red reaction, but on heating and boiling the colour does not fade. No change takes place if the tube stands for many hours. If much diacetic acid be present, this change in colour on boiling does not take place.

2. Arnold's & Lipliawsky's Test (More delicate than above)

Solutions - 1. Para-amido-aceto-phenone 1 gm.
   Conc. HCl 2 c.c in 100 c.c. water

2. Potassium or sodium nitrite solution 1%

Six c.c. of the first and 3 c.c. of the second are mixed together, add an equal volume of urine and 1 drop of ammonia. A bright red colour is produced according to amount of aceto-acetic acid present in urine. 5-2 c.c are taken and 10 c.c of HCl, 2 c.c. of CHCl₃ and 2 to 4 drops of ferric chloride added. In the presence of aceto-acetic acid the CHCl₃ is coloured violet, otherwise the colour of the
chloroform becomes yellow.
The reaction only takes place by using concentrated HCl with a specific gravity of 1.19.

3. Polarimeter Test. (very accurate)

As these bodies are leuco-rotatory, they would tend to reduce the dextro-rotatory power of the urine. The quantity of these bodies is however very small, and their specific index of rotation is negligible when compared to the dextro-rotatory powers of glucose.

Before taking a reading it is usual to clarify the urine.

10 c.c. of 10% basic lead acetate solution is added to 40 c.c. of urine, the filtrate obtained after shaking is quite suitable for observation.


To 10 c.c. of urine add 2.5 c.c. concentrated HCl and 1 c.c. of 1% sodium nitrite solution. Shake well and stand for 2 minutes. Now add 15 c.c. of strong ammonia followed by 5 c.c. of 10% ferric chloride solution. Shake up and pour into a 50 c.c. Nessler glass - allow to stand. A violet or purple colour is gradually produced, the rate at which it appears depending on the concentration of aceto-acetic acid in the urine.

(This test is not given by acetone nor by the urine of patients taking salicylates.)

Tests for B-oxbutyric Acid. (There is no very simple test for this acid.


Mix 20 c.c of suspected urine, 20 c.c. of water and a few drops of acetic acid. Boil this mixture till its volume is reduced to about 10 c.c. This drives off the acetone and diacetic acid. Add water to restore the bulk to 20 c.c. Divide this equally between 2 test tubes A & B. To A. add 1 c.c. of H₂O₂, warm gently but do not boil, for a minute. - Cool - then add ½ c.c of glacial acetic acid to each tube and a few drops of a fresh solution of sodium nitroprusside. Mix the contents and overlay the mixture in each tube with ammonium hydroxide. Put the tubes aside to stand for 4 or 5 hours. At
the end of this time compare the tubes and if the reaction be positive, tube A to which the $H_2O_2$ was added will show a purplish-red contact ring. This is due to the gradual oxidation of the B-oxobutyric acid to acetone by the $H_2O_2$.

If the tube is shaken up, the difference in colour will be seen in the fluid. The colour intensifies on standing 20 minutes or so.

The control tube B is necessary in order to see whether the acetone and diacetic acid in the urine have been completely driven off in the earlier stages of the test.

Reaction not interfered with by the presence of sugar.

2. Waldrogel's Test.

300 c.c. of urine evaporated to 100 c.c. Normal urine as control. To each add 10 c.c. of 10% sodium hydroxide solution. Stir vigorously. Normal urine does not froth while a specimen containing B-oxobutyric acid gives a distinct soapy foam. The test only indicates the probable presence of the acid in the urine.

The practical importance of qualitative urinary tests for acetone bodies has already been emphasised, but the more elaborate procedures that follow may merely be mentioned.

Methods of Investigating Acidosis and Ketosis.

The following tests are usually performed on the patient in whom acidosis is suspected.

1. Sellards qualitative plasma reaction.

1 c.c. serum is measured into a test tube and 25 c.c. of tested absolute alcohol are added. An immediate precipitate of proteins appears which is filtered off. Great care is taken to keep all the apparatus dry. A few drops of phenolphthaleine are added to the filtrate which is evaporated to dryness. All normal sera turn pink and on evaporation to dryness the residue remains red provided that it be kept hot.

In slight acidosis, the pink colour does not appear until the fluid has been concentrated. With severe acidosis the pink tint is not developed at all, but the residue of the evaporation will turn red on the addition of
tap water, and if very severe even this will fail to produce a colour.


In this method the alkali reserve is estimated in the form of sodium bicarbonate. It consists of adding acid to a measured quantity of serum or plasma, and extracting the CO₂ so produced by reducing the pressure. The fluid is trapped by a very ingenious device, and the CO₂ is measured. The alkali reserve is calculated from this volume by reference to a table. The actual CO₂ content of the blood, or else its CO₂ combining power, can be determined.

Determination of the Alveolar Carbon Dioxide Tension

(a) Haldane's method.
(b) Fridericia's method.
(c) Automatic method using a Katharometer.
Etiology of Acetonaeemia (Acetonuria & Acidosis)

(4) Conditions in which Acetonaeemia occurs.

It should be remembered that acetone is present in the urine in health in very small quantities, (1-3 centigrammes daily) but in insufficient quantities to give the colour tests.

The conditions under which the acetone bodies are increased, are essentially those in which the oxidising powers of the body are reduced by some notable deficiency, or absence of carbohydrates from the diet.

Deprivation of food, or exclusion of carbohydrates in food causes acetonuria without exception in man, also in children, during pregnancy, during labour, after injury of the central nervous system, and after the administration of narcotics such as general anaesthetics etc.

It is a fact that is usually now maintained, that the comparative starvation necessary before the administration of a general anaesthetic augments the toxic influences of the latter, causing thereby an increased formation of the acetone bodies.

Inanition or Underfeeding in health does little to impair the function of the liver, but the lowered proteolytic and glycogenic metabolism, when associated with some severe toxic agent such as Chloroform or phosphorus poisoning, causes the functional activity of the liver to become so attenuated as to endanger the structure of the
The liver cell becomes exposed to the distinctive action of its own proteolytic ferments, resulting in the formation and deposition of fat from the autolytic degeneration of the liver cells.

(a) Cyclical Vomiting.

This condition occurs particularly in children and in that respect bears a somewhat close relationship to delayed chloroform poisoning.

The children usually affected are between the ages of 3 and 12 years. The cardinal signs (of cyclical vomiting) are very constant. They are usually associated with primarily retching and vomiting, accompanied by drowsiness, pyrexia, headache, lassitude and marked muscular prostration. Abdominal pain is frequently complained of, even before vomiting sets in, and constipation is generally present although in a few cases diarrhoea accompanies the vomiting. The muscular prostration may be extreme with transient squints, loss of knee jerks, and carination of the abdomen.

Urine is as a rule acid, scanty, high coloured, and invariably contains an excess of the acetone bodies. Often the attacks are preceded by a prodromal stage lasting from a few hours to a day, with lassitude, anorexia, and headache. Sometimes a sense of chilliness or actual shivering precedes the attack, and the attacks are often precipitated by exposure and cold, change of diet,
(especially affecting the carbohydrate intake) physical or mental excitement, or fatigue.

The vomit is usually acid and towards the end of the attack is frequently coloured with bile. Attacks usually last 2 or 3 days, (but many last up to a week) and then gradually and spontaneously remit, leaving the child after a few days in normal health.

Attacks usually begin at about 3 or 4 years of age and continue at regular or irregular intervals until 12 or 13 years of age, when they tend to become less frequent and less severe. Usually at the age of puberty they have generally ceased altogether but may be replaced by migraine. In some cases cyclical vomiting begins in infancy but this is unusual and atypical.

This condition is rarely fatal, but there is definite evidence regarding the fatty condition of the liver associated with it. Longmead conducted the post-mortems in three cases dying of cyclic vomiting, in all of which fatty degeneration of the liver was present.

These conditions occur in children with an acquired or inherited nervous instability, and the excitement of the actual attack may be due to mental excitement, (e.g. parties, examinations etc) infection accompanied by pyrexia, (tonsillitis, colds, etc.) or muscular over-exertion as after vigorous games.

It has been suggested by Hilliger that all
these causes act by the over production of adrenaline, through sympathetic stimulation, and certainly all the symptoms can be satisfactorily explained by this hypothesis.

In a series of 55 cases described by Batty Shaw and Tribe, three cases were fatal. After describing the symptoms already expounded, they state that a mild degree of this condition is common, the so-called "biliousness" is a real state, a very common state, but a state that is little understood.

The following cases of my own may be cited as typical.

Case A. Leonard B. 6 years.

This boy has been seen frequently in the last few years during the attacks, and the mother states that he has had them "off and on" since early childhood. In fact she thinks they occurred in a milder degree in infancy. Interval between attacks is from 3 weeks - 3 months, but he has been free for about 6 months. He commences with a violent headache, and temperature of 101°-103.5° F. on the third day. Usually sickness begins early and the vomiting is very severe so that even water taken by the mouth is rejected. Tongue coated, but bowels may be regular. Motions are light in colour. Sickness gets more severe and finally he vomits bile and then feels better. Attack lasts 3-4 days. Urine very scanty and contains phosphates, always acetone bodies, and traces of
On examination the boy is obviously ill and extremely tender over the abdomen, but there is little or no rigidity. Usually has a very good appetite, but occasionally sick without feeling ill. Well built and active boy - rather tall - no other serious illnesses.

I have seen this boy a great many times, but of course the parents recognise the condition and do not always call in a Doctor. They are well-to-do working people and the boy gets every attention. He is an only child - rather highly strung, and excitable. The mother is of a nervous disposition and very fretty about the boy.

Case B. Eileen B. 7½ years.

This child has had attacks since the age of about 4 years, and has had them at intervals of 2 weeks - 2 months, but latterly the attacks have been much less frequent under treatment; but have lasted up to a week. (At first they were better after about 1 bout of sickness) She usually complains of feeling cold and tired. Often the following morning she vomits on waking and the vomit is usually yellow or green, and seldom food. Any food now taken is rejected, even water.

On examination looks pale and ill - temperature 100° - 103°F. - complains of pain in abdomen not localised - no rigidity. Tongue furred, and very constipated - No jaundice - Attacks usually last
about 2 days, then feels much better and very hungry. Very drowsy latterly during attacks. Urine is scanty and high coloured. Contains phosphates and acetone bodies in large quantities. No albumen. Well developed active child but very jumpy and highly strung. Keen on music. Always been more or less constipated, and continually needing aperients. Nervous mother - only child.

Case C. Kenneth W. 9 years.

This boy has had attacks of sickness since he was 3 years of age, but has not had an attack for over a year.

The mother states that the attacks started after an accident in which he sustained a fractured leg. Since then he has been very nervous and frightened in traffic. Attack starts with feeling of chill and vomiting. No wish for food and rejects even water. Usually feverish, dirty tongue, and constipated. At first attacks occurred every few weeks but has not had one for nearly 12 months. Usually ill for about 3-5 days and ends by vomiting bile and froth. After this has good appetite. Urine is always scanty and high coloured and contains acetone bodies. Always severe pain in belly and no rigidity. Well developed boy but nervous. Very fond of pianoforte. Latterly since the attacks stopped he has started rugby football and seems much better. Mother
neurotic. 2 children.

These cases are typical of a number of cases which are observed in a lesser degree of this condition. For observation purposes, I have admitted several of such cases to hospital on different occasions, but in none of them did the attacks supervene after admission, so that observations on the blood and urine before, during, and after the attacks could not be made.

In many cases the differential diagnosis between appendicitis and recurrent vomiting is almost impossible, and not infrequently children are seen who have undergone appendicectomy for such symptoms, but the attacks persisted after the operation.

The point of diagnosis is important because the child subject to cyclical vomiting is especially liable to delayed Chloroform poisoning. In some cases the appendix is responsible and in others there may be bacilluria. Probably the liver is put out of order by some toxin. Whenever the liver fails to do its work, the tissues are starved and in their autolysis produce these abnormal acids. The vomiting accentuates the condition by increasing the starvation and the loss of saline bases.

(b) Toxaemia of Pregnancy.

Hyperemesis Gravidarum & Eclampsia.

Leith Murray suggests that this acidosis may
be due to starvation produced by vomiting, and this is usually upheld by clinical experience.

The acidosis however disappears within a few hours of delivery, showing that the pregnancy is the determining factor in producing the toxaemia.

Swayne urges the abolition of the use of Chloroform when terminating the pregnancy artificially, in cases of pregnancy toxaemia. He states that since this has been done at the Bristol R. I. there has been a marked fall in the mortality in cases of eclampsia. Further (he states) many of the deaths previously occurring from eclampsia when Chloroform was used as an anaesthetic were due to coma, probably as a result of the acidosis produced by the Chloroform.

Hyperemesis gravidarum may occur at any period during pregnancy, and may begin by excessive morning sickness which steadily becomes worse. Vomiting occurs at all times of the day or night until the patient can retain nothing in the stomach. She becomes emaciated and may die of starvation. The patient may pass gradually into a state of nervous intoxication ending in coma, convulsions, and death. Urine becomes greatly diminished in quantity, and contains albumen, acetone, and diacetic acid and even blood and bile.
Cases.

A series of cases (60 in number) have been investigated which were treated by Graham in Birmingham. These 60 cases had all been sent for specialised treatment, and were all bad cases. All showed the typical bio-chemical changes associated with this condition.

Lewis Graham maintains that every case of this condition is hysterical, and the patients were treated by complete isolation in a nursing home and kept away from all friends etc.

In every case treatment was followed by cure. One case required evacuation of the uterus, where vomiting had persisted for 8 weeks without cessation. This case nearly died, but recovered, and has since had children.

That every case is hysterical is confirmed by clinical experience. It is essential to make it more uncomfortable for the patient to be sick than not to be sick. Condition is serious, as bad cases die if not cured. Bio-chemical changes erroneously considered to be the cause, and not the result of the condition.

Eclampsia is an acute toxaemia occurring during pregnancy, during labour, or in the puerperium characterised by convulsions and coma. It must be borne in mind, however, that convulsions and coma may occur during pregnancy from other toxic conditions such as uraemia and epilepsy.
The condition of the urine is of importance, and is always diminished in quantity and in bad cases may be entirely suppressed. It is loaded with albumen, hyaline, granular and blood casts are numerous and the acetone bodies are usually found.

1. In a case which I observed recently - a young woman aged 22 years had a normal labour with a midwife in attendance, but 3 hours afterwards commenced with fits of a most violent character. These fits occurred every hour for a time and continued until the next day. Water taken by the mouth was rejected. Patient was given morphia and removed to hospital. ½ grain morphia was repeated every 2 hours, and gradually the fits subsided. The stomach was washed out with weak solution of sodium bicarbonate, and 4 ozs of magnesium sulphate in water was left in the stomach. Albumen solid in urine with traces of acetone.

Made an uneventful recovery and in 14 days albumen had disappeared from urine.

(c) Diabetes Mellitus.

In Diabetes Mellitus, the acetone bodies are frequently present and are always present preceding the onset of diabetic coma.

The fact that coma has been observed to follow sudden alterations in diet, undue excitement,
great anxiety, mental shock, or severe physical fatigue, (which are themselves precursors of acetone) shows that these factors may be the direct causative agents in precipitating the final coma in diabetes. In the same way as Chloroform may, in a predisposed individual, act as the last straw in setting up post-anaesthetic toxaemia.

Cases.

The part played by infection in precipitating diabetes is undoubtedly very marked in some cases. Three cases are reported in an article in whom severe diabetes developed with a week. All these patients were children under 8 years of age, and the onset of diabetes was associated with slight febrile and catarrhal symptoms. Two of these children developed coma within 5 days of the onset of the attack. In one of the patients it was stated that the urine contained no sugar when examined 4 days before coma supervened. The other two appeared to be in perfect health until a few days before examination. Since it is well known, that infections of all kinds play a marked part in reducing the sugar tolerance in diabetes, and so increasing the severity of the symptoms, it seems fairly certain that the onset of a case of diabetes as the result of an infection, must be explained on the view that some defect already existed in the pancreas. This defect may be so
slight that under normal circumstances it did not show itself, but its existence was brought out under the detrimental action of the infection.

From time to time cases of alleged diabetic coma have been described in which the urine showed little or no evidence of the Ketone bodies. Careful consideration of certain of these cases would seem to indicate that the condition, although accompanied by glycosuria, was not really diabetic but coma from some other condition.

Begg describes some cases of diabetic coma in which there was but little ketosis though glycaemia was present. A similar condition is discussed by Payne and Poulton.

Many of these patients had really seemed to be suffering from uraemic coma; the associated diabetic symptoms did not appear to be the dominant feature. No doubt a certain number of patients with chronic nephritis have glycosuria and some ketosis, which undoubtedly accentuates the renal deficiency, but it is difficult to say that the final coma encountered is really diabetic. It is not uncommon to find uraemia coming on as an acute condition in chronic nephritis without any previous symptoms, and the manifestations of uraemia are so varied that one can hardly say there is any definite type.

(d) **Delayed Chloroform Poisoning.**

The symptoms in cases of delayed Chloroform poisoning closely resemble those met with in other auto-intoxications, e.g. diabetic coma.
It is worthy of note, that a great many observers have detected a great increase of acetone in the urine after Chloroform anaesthesia, and it seems reasonable to suppose that very possibly the blood may contain some of the poisonous precursors of acetone, and that in certain cases these are produced in so great an amount as to determine a condition analogous to diabetic coma.

That there is a possible relationship is further suggested by the very striking diminution of fatty tissue, throughout the body in rabbits poisoned by the subcutaneous injection of Chloroform. It must be remembered however, that the same rapid emaciation is also observed in animals poisoned by bacterial toxins. The most recent physiological researches on the source of acetone in the body, have disproved the old idea that it is derived from either proteids or carbohydrates, and show that fats are the true source.

If an excessive acetonuria be shown to exist in delayed Chloroform poisoning, we might hope to find in it the means of recognising milder degrees of the intoxication, and possibly also of differentiating the condition from such post operative complications as delayed shock, sepsis etc.

In many other minor states the acetone bodies appear in the urine e.g. fatigue, hunger, in certain febrile diseases, after burns and scalds, and in abnormal dietaries especially ash-free
dietaries.

Certain cases of exophthalmic goitre associated with persistent vomiting, may give the reactions for acetone etc. in the urine. Seven cases of this condition are noted by Dreachfield, and with the vomiting there is intense prostration, restlessness, and dyspnoea, occasionally followed by death.

In phosphorus poisoning, the acetone bodies are frequent constituents of the urine. It is also associated with acute fatty changes in the liver, when the organ, according to most observers, presents a condition indistinguishable from that obtained in delayed Chloroform poisoning.

These changes have also been noted after cases of poisoning by arsenic and strychnine.

In acute inflammatory conditions it has also been noted that the acetone bodies appeared in the urine.

In a case published by Routh on "Parotitis associated with Glycosuria and Acidosis", an acute attack of parotitis in an elderly man, was associated with marked acetone and diacetic acid in the urine together with a large amount of sugar. It is significant however that the acetone bodies and glycosuria entirely coincided with the severity and intensity of the parotitis, for when the acute inflammation of the gland subsided, no trace of sugar or acetone remained. So far as it is known there had been no previous adventitious
constituents in the urine, but since reporting the case there have been occasions, when a small amount of sugar could be detected, but no acetone. It is impossible to say definitely that the excretion of the acetone bodies was entirely due to the parotitis, and unconnected with the glycosuria. One is inclined to attribute the cause, to one of mild diabetes, in which the toxaemia regendered by the acute inflammation of the parotid gland, caused a temporary exacerbation of the quiescent or latent diabetes.

Source of Acetone Bodies.

Traces of aceto-acetic acid occur in normal urine - 2-4 m.gms in 24 hours. The amount is increased in starvation, (on a diet of protein) and on a diet of fat i.e. when there is a shortage of carbohydrates. The excretion of aceto-acetic acid is lessened if carbohydrates be added to the food.

The origin of the aceto-acetic acid in the urine, appears to be partly from the protein of the food, but mainly from the fat. The work of Knoop and Dakin, has shown that the oxidation of the fatty acids takes place at the B-carbon atoms; the long chains are broken down with the loss of two carbon atoms at a time.

This accounts in part for the occurrence of those fatty acids in nature containing an even number of carbon atoms. Butyric acid, if present as
such, or formed by the oxidation of higher fatty acids by β-oxidation, is oxidised and converted into aceto-acetic acid or β-hydroxybutyric acid.

Aceto-acetic acid is converted by reduction into β-hydroxybutyric acid, and vice versa, β-hydroxybutyric acid is converted by oxidation into aceto-acetic acid. It seems most likely that aceto-acetic acid, the keto acid, is the chief product of the oxidation of butyric acid.

The formation of aceto-acetic acid in the organism from fat, when carbohydrate is withheld from the food explains the formation in diabetes. Here the organism has lost its power of utilising the carbohydrates in the food, or its power of utilising carbohydrates is greatly diminished. Aceto-acetic acid is very unstable and is easily converted into acetone and carbon dioxide. This decomposition occurs spontaneously in normal urine.

The 3 closely related substances β-hydroxybutyric acid, aceto-acetic acid, and acetone, are generally referred to as the acetone bodies. There is no basis for the older statement that mild cases of diabetes excrete only acetone, that severe cases excrete acetone and aceto-acetic acid, and still more severe cases excrete β-hydroxybutyric in addition.

The occurrence of acetone in the breath of diabetics can be accounted for by the difference in the blood circulation. This is slow through the systemic system and lung capillaries, through which the blood passes before it goes to the kidneys.
Venous blood is more acid than arterial blood, so that the conditions for the decomposition of aceto-acetic acid are most favourable. Acetone is very volatile, and if decomposition occurs during the passage of the blood through the lungs it would pass into the expired air.
Treatment of Acid Intoxications.

The indications for treatment are:

(a) To prevent as far as possible the further formation of fatty acids by diminishing the fat intake, and by promoting the assimilation of carbohydrates.

(b) To break the vicious circle in autolysis, and combat acid intoxication by administration of the deficient bases. These bases will neutralise the acids already formed and prevent their further formation.

Spriggs has shown that if 2 drachms of sodium bicarbonate be given to a normal individual the urine becomes alkaline and remains so for 24 hours. But, if excess of acid is being formed this amount is insufficient, and the amount of bicarbonate that can be taken without producing neutrality or alkalinity of the urine, may be regarded to some extent as a rough measure of the degree of acid production. A more accurate measure is the amount of ammonia in the urine, which can be quickly estimated by the formalin method. In severe cases it may be impossible to make the urine alkaline.

It has also been recommended to give citrate of potash as well as sodium bicarbonate, because it is not neutralised by the gastric juice and becomes bicarbonate in the blood, where the alkali is most needed. It seems particularly
suitable in those milder cases of diabetic acetonuria in which some drowsiness, and "bilious" symptoms are present.

The advantage of citrates does not end there, since citric acid appears to diminish the production of acetone bodies.

In the recurrent vomiting of Children.

The main lines of treatment are a reduction of the intake of fat to within the limits of the tolerance of the individual child, a freer intake of easily absorbed carbohydrate, and the provision of a daily supply of alkali. The reduction of the fat intake need not as a rule be very drastic, but as children subject to these attacks are usually thin, there may be a natural tendency on the part of the parents to make matters worse by adding fat. Cream and cod liver oil are apt to be given freely and must be restricted, also the restriction of the intake of eggs and butter may be necessary, in a household where the provision of milk, cream, butter and eggs in large amounts has been considered the first essential for health and strength. The extra glass of milk often provided in the mornings should be forbidden, and milk is not recommended as a beverage although it can be allowed in puddings and in tea. Chocolate contains a high proportion of fat and is usually tolerated badly, and therefore should be omitted, as should all forms of sweets
which are rich in fat. With improvement in weight and colour these restrictions may be gradually removed.

We must especially consider the state of the child when the meal rich in fat is taken - when tired or pale, after exertion or excitement, or in convalescence after infection - fat metabolism may be especially unstable.

The fat or the excitement taken separately may not be troublesome, but the combination of the two may be sufficient to precipitate an attack. For children in the state described the provision of a free intake of easily assimilated carbohydrate is very necessary. As these children are apt at times, and in certain states to have a low tolerance for fat, there is, as a rule, a high tolerance as well as a high need for carbohydrates. Only by constant replenishment of the carbohydrate reserve, can we prevent that wasteful and imperfect oxidation of the meagre store of body fat, which manifests itself in the bout of acidosis. The digestion of carbohydrates is usually well accomplished. Many children demand these sugars but this desire may sometimes be absent, and very often the desire is strongly repressed by the parents.

Meat, fish, green vegetables, and fruit may be given as usual but the amount of sugar to be given varies in every case and in different
circumstances... All cereal foods, wholemeal bread, rusks, oatcake, sugar, jams, jelly, honey and golden syrup may be given more freely than usual. A reasonable amount of barley sugar, candy or boiled sweets, may be given daily between meals with great advantage.

Glucose powder (2 or 3 drachms) which is only about half as sweet as cane sugar, can be given three times daily in lemonade, between meals. Glucose is absorbed very rapidly into the bloodstream from the upper alimentary tract, and has not the same tendency to cause a fermentative diarrhoea.

At least two teaspoonfuls of sugar should be given in a cup of weak tea for breakfast and tea. For dinner lemonade sweetened with sugar can be given. In some cases sandwiches of bread and butter with Demerara sugar can be taken at each meal. The results of the addition of sugar are remarkable in certain bad cases. Urticaria may develop, especially where cane sugar is largely used, but clears up without any modification of the treatment, and is usually quite transitory.

Glycosuria has not been noted in any case so treated, nor is the appetite impaired by the addition of carbohydrate to the diet.

It has also been noted that the addition of a small dose of alkali daily, is often very helpful and this can be given by the addition of a teaspoonful of sodium bicarbonate to the lemon
drinks. (One daily dose).

The parents can be instructed to note any prodromal symptoms such as white stools, offensive breath, pallor, and threatened "bilious" attacks.

Small doses of grey powder, Vicky water, or other laxative saline should be administered. Barley water or lemonade, with the addition of glucose powder should be given ad lib. and this is generally well tolerated. Where, during an attack, even water is rejected, salines with 4% glucose or dextrose may with advantage be administered per rectum. Arrowroot or gruel, is also very useful and helps to prevent the production of abnormal acids.

By dietetic regulation along these lines, and by the free administration of glucose and of a small amount of alkali, good results are obtained. Increase in weight, and improvement in colour and energy, follow the subsidence of the state of acidosis. Almost always the more direct symptoms of the acidosis, and the tendency to bouts of vomiting, are definitely controlled. Any focal infection must of course be removed, and bacilluria must be treated if present. Encouragement, rest, freedom from infection, and a high intake of sugar, are most important in the treatment of this condition.
Further treatment of Cyclic Vomiting.

It may be mentioned here, that in the treatment of acetonaemic vomiting of children, insulin has been used with some success. Meyer & Bamberg report an interesting case of a boy of 6 years who was operated on, having shown the characteristic symptoms of appendicitis with specially severe vomiting. The operation did not alleviate the symptoms and the condition became worse, ultimately resulting in coma with a smell of acetone in the breath. The child seemed moribund, and his veins were so collapsed that intravenous transfusion was impossible. Glucose was given intraperitoneally, intravenously, and per rectum, together with 10 units of Insulin on 2 consecutive days; improvement rapidly occurred and the child recovered.

R. Wagner also obtained good results in cases of cyclical vomiting. E. Cameron recommends glucose with or without insulin in this condition. He explains the tendency to cyclical vomiting as due to some fault in carbohydrate metabolism in children, who respond to certain forms of stress, to infection, to starvation, to exertion and excitement, or to a diet with a high proportion of fat, and with low carbohydrate by the development of ketonaemia with diminution in the alkaline reserve of the blood, and a transitory fall in the blood sugar.
In the pernicious vomiting of Pregnancy.

In these cases there can be little doubt that the bio-chemical changes in the urine and blood are the result and not the cause of the condition, and are those which one would find in any patient suffering from starvation and constant vomiting.

In the series of 60 bad cases which I have investigated, and which were treated by Graham by the complete isolation method, there was complete recovery in every case. Only in one case was surgical interference resorted to, and the uterus was evacuated after 8 weeks constant vomiting. The evacuation nearly killed the patient, but she did recover and has since had children.

Graham maintains that every case is hysterical and they are treated by complete isolation. Confidence in the patient's medical attendant, in the nurse, and also faith that she will be cured, are essential to success. The essential thing is to make it more uncomfortable for the patient to be sick, than not to be sick, and the unpleasantness of the vomiting is brought home to the patient. Drug treatment is unnecessary except for the administration of potassium bromide at night with milk. Dieting is light but not greatly restricted and fluids are administered ad lib. The addition of glucose, and extra sugar to the diet is helpful, but has not the striking effect that is
found in the treatment of cyclic vomiting in children.

Encouragement and treatment by psycho-therapy, has had good results in certain cases and in conjunction with isolation might be very helpful.

Some observations by Longridge, on eclampsia show that the same general line of treatment as in other forms of ketosis may be helpful. He noticed a diminution of the alkalinity of the blood, and gave citrates with the object of increasing the alkalinity. Sugar was also given by the mouth and rectum.

Further Treatment of the Toxaemias of Pregnancy

(Insulin).

The intravenous injection of glucose solution has for some time been gaining favour among Obstetricians, for the treatment of the toxaemic conditions of pregnancy viz: hyperemesis gravidarum, eclampsia, and pre-eclamptic states, which are accompanied by a distinct acidosis, and the application of Insulin therapy to such conditions seems a logical sequel.

Levy has employed the combination of glucose and insulin with marked success. He holds that the acidosis which is prominent in the later stages of pernicious vomiting, is not only the result of the stomach's intolerance of food, but also a factor in
producing the acidosi, and that, if the resulting vicious circle can be broken either by abortion, which removes the toxin of pregnancy, or by the correction of acidosi, good results may be expected. If the vomiting is not checked a starvation acidosi results. It is important to distinguish between true eclamptic toxaemia, and purely renal conditions, since in the latter glucose and insulin are useless. His method of treatment is to give 500-1000 c.c. of 10% glucose solution intravenously, with 1 unit of Insulin hypodermically, to each 3 grams of glucose, administering one-third of the amount of each, at a time, until the whole has been given and injecting the solution slowly. He holds that the blood sugar is not increased in eclampsia, and that insulin alone as recommended by some authorities is therefore dangerous.

It appears necessary amply, to cover the glucose equivalent of the insulin injected, since the improvement is not only due to combustion of carbohydrates, but also to its storage as glycogen in the liver. For this reason glucose has been advocated alone, but the consensus of opinion favours the simultaneous use of Insulin since it is probable that this aids glucose storage as well as its combustion. Improvement as a rule is quicker with Insulin and glucose, than with glucose alone.
Continental authorities including Vogt, have employed insulin alone with successful results, but for the reasons already given, it seems that the combination of Insulin and glucose is a more rational treatment, is safer and gives better results. With regard to the practical value of Insulin treatment in the toxaeemias of pregnancy, Vogt concludes that the combination of Insulin and glucose is the best treatment, and that it provides a new and valuable method of treating these conditions. He holds that, before pregnancy is artificially interrupted, this form of treatment should be given a trial and that it is certainly the best for simple eclampsia.

In post-anaesthetic vomiting.

Before operation on even apparently healthy children, careful inquiry should be made as to the history of "bilious" attacks, which may in reality be those of acidosis. Whenever possible, operation on a child should be delayed until it is accustomed to the altered diet of hospital (of course this is impossible in emergencies and in minor operations). The urine should be examined for albumen and diaetic acid.

Both starvation and fright cause acidosis - four hours fast before operation is too long, and a maximum period of 3 hours is suggested since the last feed, which should consist of dry toast and weak tea.
Saline enemata containing 2% - 5% of dextrose or glucose should be given after the lower bowel has been cleared - 2 hours before, and soon after operation. The effect of fright cannot be altogether controlled but may be diminished by preventing starvation.

Pre-operative ingestion of barley sugar is a valuable prophylactic measure, much appreciated by the patient and is a much easier method of administering carbohydrate.

Should symptoms of acidosis occur despite these precautions, dextrose must be administered in some way.

Beddard recommends that if it cannot be retained in the stomach it should be given by continuous rectal infusion of 10% - 20% solution, or even by infusing a 5% solution intravenously. Once toxic vomiting has become established, sodium bicarbonate, and other alkalies, must be given freely to neutralise the acids already formed.

Treatment by Insulin.

This post operative acidosis has long presented a difficult problem both as to the origin of the acidosis, and the extent to which the acids present are dangerous. It is believed that this condition depends on the nutritive disturbances caused by the anaesthetic, (especially chloroform) in which functional inefficiency of the liver plays a large part.
In the treatment, Insulin has been lately used and with some success, the rationale of the treatment being, that there is a pathological analogy between the metabolic effects which lead to this acidosis, and that occurring in diabetes.

On the theory, that in shock, there is an internal or cellular asphyxia and acidosis, with checking of oxidative processes and resulting exhaustion, and that this state is primarily caused by a sudden derangement of the central nervous system, is based a recent treatment of this condition.

Fisher recommends the injection of 500 - 2000 c.c. of a sterile 10 - 15% glucose solution intravenously, the total duration of the administration being 1 hour, and preferably 2 - 4 hours. For every 3 gr. of glucose injected 1 unit of insulin should be used, the total amount being divided into two equal doses, and one part being given about 15 minutes after administration of glucose has started, and the remainder at the end of administration. As long as sugar appears in the urine there is no danger of a reaction.

By the above method Fisher has successfully treated 31 cases of this condition, and he has also used it with gratifying results as a prophylactic measure in the pre-operative preparation of surgical cases, when the subject was not a good surgical risk,
and also to check the incessant vomiting of acute peritonitis.

Claudia Potter confirms the good results obtained with Insulin-glucose treatment in post operative acidosis, especially post anaesthetic vomiting. From the results of 185 cases in which it was given she concludes that this treatment appears to be a very powerful remedy for post-anaesthetic vomiting.

The glucose is given by mouth or rectum, 30–40 minutes before operation allowing at least 2 grains of sugar for each unit of Insulin when given by the mouth, or 3 grains when given by rectum. 5 units of Insulin are injected hypodermically, 20–30 minutes after glucose by mouth, and 40–50 minutes later if it is given by rectum. In severe cases requiring glucose intravenously, 10 units of insulin are given about 10 minutes later, but it is stated that this method is not advisable unless vomiting is persistent, and fails to yield to the use of insulin with glucose by mouth or rectum.
Summary and Conclusions.

In summarising the points brought out in this thesis, it may be necessary to point out that although the condition of acetonaemia is considered mainly in children, it was found essential to consider analogous conditions occurring at other stages of life.

In understanding children, one must remember that the metabolic processes of children, just because they are children, are less stable than they become in later life. In this instability, we may find partly the explanation of the greater frequency in childhood of many disorders due to biochemical derangement. Infancy and childhood, differ from all other periods of life in being pre-eminently the time of rapid development, both physical and mental.

The peculiar liability of the nervous child to these derangements of metabolism, especially to the condition known as acidosis, is not only a direct result of his undue sensitiveness to emotional excitement, or physical fatigue, but the state of disordered metabolism so produced, is of itself, provocative of the symptoms for which our advice is sought. The nervous child is more prone to acidosis, and whenever the symptoms of acidosis are recognisable there is apt to be a simultaneous exacerbation of all the nervous symptoms. There is
no doubt also that the psychological factor may play some considerable part in the causation of this condition, and at least part of the nervous diathesis may be due to the unhealthy psychological atmosphere of home life.

In certain diseased conditions such as Addison's disease, where the suprarenal glands are destroyed by caseation, there is often a state of hypoglycaemia accompanied by great vaso-motor weakness and pallor, a low blood pressure, rapid pulse, extreme amyotonia, and attacks of nausea and vomiting. We know that the suprarenal glands are exhausted, and that their function becomes impaired under the stress of great infection. These are the same conditions which lead to the exhaustion of the carbohydrate reserves, and they are the same conditions which in practice we are forced to regard as productive of the prostration and vomiting of the nervous child.

It is possible that in Addison's disease we are observing the effects of the gross destruction of the suprarenal tissue; in an attack of cyclical vomiting we are encountering the temporary exhaustion, and functional impairment of the same glands. The failure to mobilise by means of the suprarenal glands, sufficient carbohydrate to achieve the complete metabolism of the absorbed fat, is in all probability the true explanation
of these attacks, which are so variable in their individual symptoms.

That in most cases, the mobilisation of the necessary carbohydrates is in the end successfully achieved, spontaneously and somewhat suddenly, after an interval in which the child may suffer extreme distress, is in keeping with the hypothesis that the suprarenals have become temporarily exhausted.

In many cases of cyclic vomiting, without any treatment, the symptoms which up to a point have been progressive and threatening, suddenly subside; there has been delay in the necessary mechanism for carbohydrate mobilisation. It can be shown that there is not a progressive fall of blood sugar culminating in an attack. The blood sugar may even remain normal right up to and during the early stages of the attack, though later it may fall quite suddenly to a low figure, not necessarily with any increase in the symptoms.

The remarkable effect in controlling and preventing these attacks of recurrent vomiting, by such a simple alteration in diet, and the exhibition of sugars as indicated, is very striking.

In the last few years I have followed up a good many children who have been prone to attacks practically since birth. Under treatment and general management the attacks have been lessened
and in many cases have disappeared completely.

Recently attention has been drawn to the fact that the "pre-rheumatic" child often gives a long history of various symptoms of ill-health, which are believed to be intimately and causally related to the incidence of rheumatic fever among young children. These symptoms are almost identical with those found in children suffering from a relative insufficiency of sugar in the diet. Therefore it is possible that in such cases the dietetic modifications indicated, afford a means of preventing acute rheumatism, or at least of diminishing its frequency.

Again, the part played by acidosis in the production of attacks of asthma in childhood, or at least in the determination of the moment when an attack comes on, has not been sufficiently emphasised. A large number of asthmatic children also suffer from recurrent attacks of vomiting in greater or lesser degree. In the part played by glycopenia, we have perhaps, the explanation of the tendency, common to both disorders, to nocturnal exacerbations. Such children stand the physiological starvation of the night badly, and in the absence of a frequent intake of sugar, the nocturnal metabolism is relatively unstable.

In practice, it is often found that successful control of the acidosis brings with it
cessation of the asthmatic attacks, or at least a diminution of their number.

The following conclusions would appear to be justified:

(a) Cyclical vomiting occurs mainly in "nervous" children, attacks usually being precipitated by mental stress of varying kinds.

(b) Cyclical Vomiting is common among children of all classes, in major or minor degree.

(c) It is due to depletion of the glycogen reserves of the body, mainly the liver.

(d) Dietetic regulation, free administration of glucose, reduction of the intake of fat, and provision of a daily dose of alkali, lessen the frequency of the attacks, and in many cases prevent their recurrence.

(e) A large proportion of cases of "debility" may be due to sugar shortage.

(f) The recognition and treatment of the pre-rheumatic state, may make our efforts to prevent and control rheumatic fever in children more effective; marked similarity of this pre-rheumatic state with that due to an insufficiency of sugar in the diet.

(g) A number of children with asthma suffer from cyclic vomiting and the successful control of the acidosis brings with it a cessation of the asthmatic attacks, or at least a diminution of their number.
(n) Acetonaemia in other conditions associated with vomiting is secondary to the vomiting and the exciting cause may be nervous in origin, or due to causes such as poisoning or starvation etc.
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