Acetonuria and Acidosis,

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Acetonuria and Acidosis:

In the following paper an attempt will be made to describe the present state of opinion regarding the cause, and conditions of occurrence of aceton bodies in the urine, and to classify and describe the various cases which, from a consideration of their symptoms, physical signs and pathology, deserve to be classed under the generic title of acidosis.

In the first place I shall give a brief description of the physical characters and chemistry of these aceton bodies, and then describe briefly the most useful tests for their detection in urine.

The substances included under the title aceton bodies are three in number viz., Bocyteic acid, diacetic acid and acetone.

Bocyteic acid, \( \text{CH}_3\text{CHOHCH}_2\text{COOH} \) by oxidation becomes diacetic acid \( \text{CH}_3\text{COCOCH}_2\text{COOH} \) which in its turn by loss of \( \text{CO}_2 \) becomes acetone \( \text{CH}_3\text{COCH}_3 \).

All three are readily soluble in water, alcohol and ether. Hammarsten describes them as follows: acetone is a thin clear liquid with a pleasant fruity
The Acetone Bodies:

Odour and is lighter than water.

Glutaric acid is a colourless strongly acid liquid which, on being heated to boiling with water, especially water to which some acid has been added, decomposes into CO₂ and acetone.

Pyruvic acid usually forms an odourless syrup but may also be obtained as crystals.

From the above statement of the chemistry of these bodies it is evident that a very close relationship exists between them.

Normal urine contains a faint trace of acetone, or faint that special processes are required for its detection and we therefore conclude that a pathological acetoneuria is present if we get a positive reaction by any of the ordinary clinical tests.

The two most valuable clinical tests for acetone at our disposal are Legge's U. potassae test and the liqour ammoniaci test.

1. Legge's Test. The best method of performing this test is as follows:

To about 1 ccm of urine add a sufficient amount of liq. potassae to render it thoroughly alkaline; it will frequently be found necessary to add almost as much liqur
Regal's Test:

potassae so there is urine before the mixture is thoroughly alkaline. To this mixture add a few drops of a strong solution of sodium nitroprusside; this is prepared by dissolving a few crystals of sodium nitroprusside in a test-tube full of water by the aid of heat till a deep red solution results.

On addition of the few drops of sodium nitroprusside solution a bright ruby red solution results. To this a few drops of dilute solution of acetic acid are now added, and if acetone be present a purplish red or claret colour results varying in depth according to the amount of acetone present. This test has no real fallacies though Hammersen states two which might easily cause some confusion to a very unskilled observer; these are creatinin which gives a yellowish color changing to green on the addition of the acetic acid; and para cresol which gives a faintish colour on the addition of the acetic acid.

2) The liquor ammoniacæ test has only recently come into prominence and has recently been described by Wilcox, Jackson, Taylor, and Cambridge. The method which follows is practically the same as that at-
Liquor Ammoniae Test:

- Take about 1 inch of suspected urine in a test tube. If the urine is neutral or alkaline, acidify with dilute acetic acid. Then add enough sodium metabisulphite solution to give the mixture a distinct bright red colour. On this basis, this mixture faintly caresea a layer of liquor ammoniae, fending about 1 inch thick. If acetone be present a beautiful magenta nip will appear at margin of contact of fluids gradients, diffusing itself up through the layer of liquor ammoniae. If a large amount of acetone is present, the colour reaction appears at once but if only present in small amount, it may be a minute or two before the magenta colour appears.

It will be noticed that I emphasise the necessity of having the urine acid before proceeding to the test. This point seems to have escaped the attention of those who have previously written on the subject. The reason is that the colour reaction is much more striking if the urine is acidified. As a matter of fact, it is rarely necessary to acidify the urine as acetone bodies almost invariably occur in acid urine but I have myself, on several occasions,
Liquor Ammoniae Test:

detected the presence of acetone in neutral urine.

If the urine is already acid we should never add any further as acetic acid, sodium nitroprusside and liquor ammoniae form when added to a solution containing creatinin give a purplish coloration which might easily be mistaken for reaction due to a trace of acetone.

If we perform the above two test as a routine performance the only case in which we can be in any doubt concerning the presence or otherwise of acetone is when only a faint trace of acetone is present.

When we are in doubt in such a case we may make certain by adding enough liquor potassae to 1 inch of urine to render it alkaline then adding enough saturated solution of iodine in Potassium Hydrate to just saturating mixture a Watery colour.

Heat this mixture and examine yellowish precipitate resulting for crystals of iodoform. If the microscopic examination of the precipitate reveals iodoform crystal we may be quite certain that the urine contains acetone.
Comparative Value of Regal's and Liquor Ammonia Tests.

Some time ago I performed Regal's and Liquor Ammonia tests with known solutions of acetone in order to gain some idea of their absolute and relative delicacy.

With regard to Regal's test I found that when the dilution of acetone exceeded 1 part in 400, the purplish coloration ceased to appear; much a slight darkening was observable but sufficiently distinct for clinical purposes.

In the case of the liquor ammonia test a fairly definite purplish ring could be observed up to a dilution of 1 part in 320. Beyond this dilution the test was not reliable. I also found that in order to obtain the maximum degree of delicacy of the test the acetone solution had to be previously acidified.

Of course, this is usually unnecessary in urine testing as acetone bodies almost invariably occur in acid urines.

The general conclusion to which I came was that both tests were quite delicate enough for clinical purposes and that in the whole Regal's test was preferable to the liquor ammonia test as being slightly more delicate and presenting less possibility of confusion owing to the presence of creatinin in the urine.
Test for Diacetii Acid:

To 1 c.c. of freshly-unboiled wine add a solution of Ferric Chloride of a pale sherry colour till a precipitate of phosphate of iron ceases to fall. Add a few more drops of ferric chloride solution and if diacetee acid be present a burgundy colour will result. A somewhat similar but darker colour may be produced if salicyrnic, salicylates, carbolic acid, acetic acid, formic acid or thallium are being secreted in the wine.

To make certain that it is really diacetee acid which is present now boil the wine before performing the above test. If the reaction is about or much less than before diacetee acid is present; if it is marked as before it is one of the above mentioned substances. This depends upon extreme readiness with which diacetee acid when boiled in presence of water becomes converted into acetone and carbon dioxide. This is also why it is properly stated above that in performing the test the wine must be fresh and unboiled.
Acetonuria.

Illustrative Cases.

Acetonuria is present and I there proceed to show that such an acetonuria is exceedingly common especially in children.

While House-Physician at Paddington Green Children's Hospital in London, I systematically examined all the urines of the cases under my charge for acetoone bodies.

In every in-patient in whom it was possible to obtain regular specimens of urine, sometimes a matter of extreme difficulty in children, the urine was examined every few days for acetoone and diacetic acid. If acetoone bodies were found, the urine was, as far as possible, examined daily.

In all, the urines of 153 cases were examined; in 43 of these (28%) acetoone was present; out of the 43 cases, diacetic acid was present in 13 and in 8 out of the 13 cases there were symptoms of acid poisoning.

It may be stated here that in great majority of cases in which Acetonuria appears, the acetoone is present in large amount; thus, out of the 43 cases of Acetonuria, the colour reaction to both tests was a very marked one in 30 cases corresponding to a proportion of acetoone certainly not less than ½ – ⅔ as compared with
Acetonuria:

The reaction yielded by an acetone solution of
known strength.

Acetonuria as will be seen later is due to defec-
tive fat metabolism.

The two great causes of defective fat metabolism
are want of oxygen and toxemia of some
sort.

Oxygen deficiency may be due to many causes; the
chief being insufficient aeration of the blood
such as we get in a bad case of broncho-
-pneumonia or insufficiency of carbo-
-hydrate in diet or inability to digest them.
The latter is specially emphasized by Von
Wooden. He shows that the value of carbohydrate
rate feeding in checking acetonuria is mainly
because of the large amount of oxygen present
in carbohydrates.

The toxemia may be due to many causes and
the poison may be either injected or
produced in the body as the result
of intestinal disturbance, sepis etc.

Now let us see if an analysis of the
above mentioned cases of acetonuria will
bear out these statements.

In 13 cases there was a well-marked
-gastro-intestinal derangement. 9 of these
Acetonuria - Analysis of Cases:

were simple cases of gastro-intestinal disorder, some with vomiting, some with preceding constipation but most of them had diarrhoea and loose foul motions; in 3 cases symptoms of acid poisoning were observed.

With milk diet and free fermentation the stools returned to normal and the acetone bodies disappeared from the urine.

There were cases of Tuberculous Peritonitis in all of which the stools were loose and off-ensive; in these cases also the acetone bodies ceased as soon as the stools became normal but under careful dietary measures.

One was a case of colitis with loose offensive stools with a large admixture of mucus. On admission the urine contained a large amount of acetone but under treatment by purgatives and frequent washing out of bowels the stools rapidly became more healthy and in three days the acetone bodies had quite disappeared from the urine.

Two were cases of Natriuria. Now natriuria is admitted to be due to absorption of poisonous substances from the bowels in consequence of unsuitable food. Under careful dieting the eruption disappeared in both cases and at the
Acetonuria — Analysis of Cases:

t ime the acetonuria ceased.

In the above thirteen cases it will be seen that there was a definite gastro-intestinal disorder associated with the acetonuria and that the acetonuria ceased in every case when the gastro-intestinal tract returned to a healthy state.

Then there were five cases in which the poisoning was evidently due to the absorption of organical toxins — these were cases of Epidemic Summer diarrhoea and all three presented an appearance of profound toxemia. Two recovered and so the state returned to normal the acetonuria ceased. The other two were cases of Post-Diphtheritic Paralysis. On admission both had well marked acetonuria — after admission the acetone bodies gradually dis-appeared and ceased in the course of five or six days. Probably the diphtheria itself was to blame for the derangement of metabolism in these cases. In proof of the likelihood of this we may instance the experiments of Botazzi and Crepici, who injected antitoxin into children suffering from diphtheria.
Acetonuria - Analysis of Cases:

and had well-marked acetonuria. In all the curve of aceton excretion showed a sudden fall after the administration of the serum.

In two cases there was a localized focus so that the acetonuria was probably due to local absorption. These included two cases of pyelitis, 1 bulilitis, 1 chronic pyelonephritis, and 1 subacute nephritis in which the urine in addition to albumin contained also a large amount of pus probably from a co-existent pyelitis. In all the cases except the pyelitis the condition gradually improved and the improvement was followed by disappearance of the acetonuria.

Well marked acetonuria was also present in 1 case of Subacute Rheumatism and in 3 cases of Acute Rheumatism. All four were being treated with potassium salicylate which, as I shall show later, is a recognised cause of acetonuria and salicylate poisoning. It is also probable that there may have been a factor of organic origin in the three cases of Acute Rheumatism due to the possible rheumatism. Langmead suggests in his paper on the subject of Salicylate Poisoning in Children.
Acetonuria - Analysis of Cases.

Then there were two cases of Cyclic vomiting. These cases will be discussed in detail later on, but we may say at present that they are generally recognized to be due to breakdown of the mediating power of liver, especially that there is usually a large nervous influence in these cases, and that a frequent exciting cause of the attacks is some gastro-intestinal disturbance.

Two were cases of Tuberculous Meningitis. The exact causation of acetonuria in these cases is somewhat obscure but it probably has something to do with the diminution in oxidation and general metabolism which is present in a comatose or semi-comatose patient. It is possible that the change in most of metabolism may be partly due to a nervous influence in these cases.

In all cases there was evidence of marked deficiency of oxidation; these included full cases of Broncho-Pneumonia and one case of Lobar Pneumonia.

In one case the deficiency of oxygen was due to insufficiency of carbohydrates. It was a case of Diabetes Mellitus in which the urine was quite normal on admission.
Acetonuria - Analysis of Cases:

When the patient was put on restricted diet, a small amount of acetone appeared in the urine and persisted as long as the restricted diet was continued.

In two cases no evident cause for acetonuria could be found. Three cases of renal, anuria and acute anterior polynephritis, in 5% there was only a small trace of acetone present which might have been due to some slight cavity overlooked cause. This was one of the forty-three cases in which acetonuria existed; a quite definite cause for the condition was present in the great majority.

To recapitulate: out of the 43 cases, in 13 a definite gastric intestinal Disturbance was present; in 5 there was evidence of an organismal toxemia; in 5 probable absorption from septic processes; in 4 sodium salicylate was being administered; in 5 there was definite diminished oxidation and in 1 the carbohydrates in the diet were insufficient in quantity.
Causes of Acetominuria:

2 were cases of Cyclical Vomiting;

5 were cases of Tuberculous Meningitis in which there was probably a strong nervous influence combined with a general deficiency of oxidation.

It will be seen therefore that twenty-seven of the forty-three cases were probably due to some variety of poisoning.

Below will be found a short list of the more common conditions in which acetominuria is found. It is compiled from the writings of Langanon Brown, Langmead, von Jauck, Von Nutten, and from my own experience.

Toxemia:

Auto-intoxications: all varieties of gastric intestinal disturbance.

Organismal toxemia: anthrax, pneumonia, pydemic diarrhoea etc.

Drug poisons: Phosphorus, morphine, chloridgin, sodium salicylate, chloroform, ether, ethyl chloride, nitrous oxide.

Deficiency of oxygen:

Insufficient pulmonary aeration: Broncho pneumonia, Acute lobar pneumonia, Mumps, etc.
Deficient injection or utilization of carbohydrates.

Abnormal, inadequate, diabetes mellitus, fever, etc.

Influence from Nervous System important.

Cyclic vomiting, Meningitis.

Source and Mode of Production of Acetone Bodies

The source of acetone bodies has long been a matter of dispute. At first it was almost held that they were universally elaborated from proteins but this theory has been now discredited as I shall proceed to show.

It is evident that acetone bodies must be elaborated from one of the three great groups of food and tissue material, i.e., either from carbohydrates, proteins, or fats.

As the actual source of acetone in the human body we can at once put carbohydrates out of count for following reasons. It was first established by Hirschfeld and Rosenfeld, and is now universally admitted that after the immediate and invariable result of the exclusion...
of carbohydrates from the diet, is the appearance of acetone bodies in the urine. In such a case the amount of acetone bodies gradually increases for some days and then diacetic acid and later 3-oxobutyric acid begin to appear as oxidation becomes more and more defective.

If now carbohydrate feeding is restored, the acetone bodies will rapidly diminish and disappear, the less highly oxidised products disappearing first.

A peculiar clinical example of this fact will occur to everyone: if a patient suffering from diabetes mellitus is put on a restricted diet acetone bodies frequently appear in urine, while, if put on a carbohydrate-free diet, acetonuria invariably develops.

We may conclude therefore that carbohydrates are not the actual source of acetone bodies but must admit, from the fact that absence of carbohydrates in the diet causes acetonuria and vice versa, that they must play an important role in aiding the metabolism of the materials, whether fat or protein, which is the actual source of acetone.
Source of Acetone.

From the fact that acetone almost immedi-
ately appears on carbohydrates,
the being excluded from diet while the
less highly oxidised products, dextrose,
acid, and pyruvic acid do not
appear for several days, it would seem
that absence of carbohydrates results in
a defective supply of oxygen to the
metabolising tissues and therefore it
is exceedingly probable that Von Noorden
is right when he states that the virtue
of the carbohydrates rests in the large
amount of oxygen which they contain.
Having excluded the carbohydrates, we are
now left to choose between the protoids
and the fats.

It will perhaps be better to dispose of the
protoids first.

Both Von Jaksch and Von Noorden state that
acetone bodies can be produced experiment-
ally from either carbohydrates, fats
or protein, the intermediate product in
all cases being butyric acid.

In pursuing investigations as to the source
of acetone bodies we can hope to get no
help from experiments on animals because
Source of Acetone.

As Hammarsen stated, the conditions in them are quite different. He instances the dog in which acetone is produced by starvation and not reduced by carbohydrates feeding, while the curve of acetone excretion runs parallel with the curve of nitrogen excretion. In all of these particulars the dog is quite different from the human being.

The evidence in favour of the elaboration of acetone bodies from proteids is merely a mass of theory and conjecture without one definite incontrovertible fact, while there are several very strong facts against the origin of acetone from proteid material.

As stated above, acetone bodies can be produced from proteid material experimentally.

Von Jaksch states that they originate in proteid material and quotes Becker who thought that post anaesthetic acetoneuria was due to breaking down of proteid.

He also quoted Vincenelli and Knapp, who states that acetoneuria only occurred in pregnant women after the death of the foetus. Von Jaksch thought that breaking down of proteid material of foetus was responsible for acetoneuria in these cases.
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Source of Acetone:

This statement of Briarelli and Knapf was however disproved by Stolz who found acetonuria in pregnant women quite apart from death of foetuses.

It was also thought by many that acetonuria occurring during starvation, fevers, diabetes, digestive disturbances was due to breaking down of proteins.

The above are the main facts which have been adduced in favour of the origin of acetone bodies from protein and it will be seen that apart from experimental production of acetone bodies from protein, the other instances are merely matters of opinion and the acetonuria in the embryo given might quite as well be due to breaking down of fats.

The fact may be stated here where is well with conclusions against the origin of acetone bodies from protein. This has been particularly pointed out by Langdon Brown and Hammarsten. They both state that in acetonuria no relationship exists between the amount of acetone bodies excreted and between excretion of nitrogen and sulfur, it was should expect to find...
Source of Acetone

If protein material were the source of the acetone bodies. The credit of this discovery belongs to Weintraub and Salina. How let's us see what evidence we possess that fats are the source of acetone bodies.

In the first place acetone bodies have been produced experimentally from fats. They have also, it is true, been produced from proteids but butyric acid, which is the precursor of Butyric acid (the least highly oxidised of the acetone group), is a fatty acid and therefore much more simply elaborated from fats than from proteids.

Von Noorden, after carefully weighing the evidence for and against the origin of acetone bodies in fats, decided in favour of fats and gave the following proofs in support of his views — In 1897 Beechey found that administration of fat in food increased previously existing acetomuria. In 1898 Runn said found in a case of diabetes mellitus that acetomuria only developed after he had given the patient Butyric acid. In 1899 Magnus levy decided in favour of
fat on finding, in a case which he investig-
atied, that more acetone was produced than
could possibly have been elaborated even
if maximum possible catabolism of
protein had taken place during period of
investigation.

The occurrence of acetonuria in inanition
and in fever, diabetes, digestive disturbance
and other conditions associated with
inanition has been frequently cited as a
proof of the origin of acetone from prot-
elaid. But all these conditions are rather
in favour of the origin from fat because
it is a well-known fact that in inanition
the tissue which is most largely
broken down is the body fat.

Hirschfeld and Schwartz after carefully
investigating the subject both decided
that fat was the main source of acetone
bodies.

In fatal cases of Acetone Bounting and
Post-anesthetic Poisoning the livi shows
an extreme degree of fatty change and
some organs such as the kidneys and
heart may also show some fatty change.

New Peters state emphatically that this
Source of Acetone:

The so-called "fatty degeneration" of liver is not a degradation conversion of the proteins of the hepatic cells into fat, but that in fatty liver and heart the fat has been transported from the connective tissues in order to supply the liver and heart with energy but that the metabolic processes necessary for the complete metabolism of fat fail and fat accumulates, causing the so-called "Fatty Degeneration".

Langdon Brown also calls attention to this fact and suggests the use of the term "Fatty Congestion of the Liver".

These are emphatically cases of poisoning by less highly oxidized acetone products as will be shown later, and the urine is always loaded with acetone and diacetic acid. Taking this into consideration, even the fact that a condition of liver is such as we should expect if fat metabolism breaks down, we are justified in regarding these cases as very strongly in favour of origin of acetone bodies from fat.

From a physical of the above statements it will be evident that acetone bodies are
Role of Carbohydrates in Fat Metabolism

due to imperfect metabolism of fats, if not in all cases, at least in the very great majority of them.

Reference has already been made to the fact that the withdrawal of carbohydrate material from the diet invariably causes acetonnuria which at once disappears on the resumption of carbohydrate feeding.

It is evident therefore that carbohydrates must in some way be intimately connected with the metabolism of fats. At first sight it would seem likely that the role of the carbohydrate rate was simply that of a fat-sparer. Von Noorden, however, investigated this point and found that the discrimination of acetonnuria taken carbohydrate administration is resummed in much greater than would be the case if the injected carbohydrate merely took the place of a proportionate amount of fat. He therefore concluded that virtue of carbohydrate material rests in its relative abundance of oxygen—this oxygen is drawn on to complete the oxidation of fats so as to reverse in the end products of fat metabolism namely carbon dioxide and water.
Role of Carbohydrates in Fat Metabolism.

This view is supported by Vernon who
thinks that tissue oxidation is carried
on by non-nitrogenous groupings probably
of a carbohydrate nature which are not
even in chemical combination with prot-

Thus it comes about that, if carbohydrates
in diet are insufficient, defective oxida-
tion of tissues occurs and we get
defective fat metabolism causing the app-

pearance of acetone bodies in the urine.

The Normal Metabolism of Fats is thus
described by Von Wostrow and we may take
his description as embodying the latest view
on the subject.

The state that from tissue fats we
first of all get Butyric Acid which
is oxidized to form Butyryl Butyric Acid.

At this point the carbohydrate comes
into play; if they are present and oxid-
ation consequently satisfactory, the chain
between the A and B carbon atoms is
broken, one half of the chain being oxida-

ised and the other reduced, resulting
in two molecules of Acetic Acid
which are oxidised and produce Carbon
Normal Metabolism of Fats:

dioxide and water.

If however the carbohydrates are absent or present in insufficient quantity, the first half of the chain is oxidized but the second half not produced so that acetic acid is produced which by loss of Carbon Dioxide becomes Acetone.

These views are, of course, largely theoretical but as for they express the best of our knowledge on the subject.

Acidosis or Acid Poisoning:

When fat metabolism is very much interfered with somehow so that most of the fat is not oxidized beyond butyric acid, we get a constantly increasing amount of this acid circulating in the blood and excreted in breath and urine. Such a patient always shows some signs of poisoning.

So the symptoms resulting from this condition the name of Acidosis or Acid Poisoning has been given.
Acidosis: Symptoms:

It follows that any condition which can produce diacetic acid may also produce a greater or lesser degree of acidosis if severe enough.

In a case marked as acidosis the clinical picture is a very striking one but the great majority of cases which occur are very much slighter and are very liable to be wrongly diagnosed unless a sharp lookout is kept for symptoms of the condition.

Take a child who is suffering from pronounced gastric intestinal disorder and whose urine contains acetic acid. Such a child is frequently very drowsy and lies curled up in bed not taking any interest in what is going on around about. If interfered with in any way, as for example by the examination of the doctor, the child objects strongly and is very irritable and excitable. On smelling the breath it will be found to have a faint aromatic fruity odour very suggestive of acetone and on examining the urine it is found to contain a large amount of acetone and occasionally a trace of diacetic acid. Such a child is undoubtedly suffering from a slight degree of acid poisoning and the urine is con-
Acidosis: Symptoms

pillared by the suddenness with which the little patients return to their former
bright intelligent condition as soon as
the aetonuria ceases.

From these slight cases we get all gradati-
ons till we come to the fully developed
cases in which one or other of the cardinal
symptoms, torpor, vomiting, or delirium,
may predominate.

In some vomiting frequent long-continued
and very severe is the prominent feat-
ure while the drowsiness is less marked.

In others we get a gradually increasing
condition of torpor which may or may
not alternate with sudden wild delirium
or attacks of vomiting and while gradually
deepens into absolute coma.

The breath always smells strongly of acetone
and the urine is loaded with acetone
and frequently contains diabetic acid
in considerable amount.

These fully developed cases are very
frequently fatal.

All the various forms of acidosis
will be described later, the principal
forms being as follows.
Forms of Acidosis:

1. Cyclic vomiting
2. Post anaesthetism Poisoning
3. Salicylate Poisoning
4. Diabetic Coma
5. Cases associated with gastric intestinal disturbance
6. Some of severer forms of Pregnancy vomiting

It is a well-known fact that in really fully developed cases of Acidosis a fatal issue is almost invariable — recovery from fully developed Diabetic Coma or Post Anaesthetism Poisoning is almost unknown.

As a practical clinical example let us take a very marked case of Diabetic Coma. If we adopt transfusion of a large quantity of Sodium Bicarbonate solution in such a case, we frequently drag the patient back to consciousness for a few hours; but they invariably relapse into coma deeper and pass on to a fatal termination. The reason for this is simply that we have neutralised the acid present in the blood at the time of transfusion but have done nothing to
Nature of Acidosis:

Once a condition of acidosis is fully developed, it tends to increase rapidly because, as a result of the circulation of blood, the neutrality of the medium is seriously reduced. Less and less carbon dioxide is consequently taken up from the tissues which are thus gradually dehydrated. Acidification is diminished, and diminution of the tissues, in precisely the condition which is most detrimental to fat metabolism and is therefore fed on, highly oxidised products produced. It is more acid, more acetic acid, and so we get a sort of vicious circle, produced causing the patient to fall rapidly into deeper coma. From the above description Acidosis would appear to be a comparatively simple affair. But the opinion is at present gaining ground that in well-marked cases of Acidosis at least, there is another fact—so at work and most authorities incline to the view that the liver is at fault. Many things point to this. The liver is here known to be one of the most important seats of metabolism of carbohydrates.
Acidosis: Autolysis

23. Schoeniger states: When the food supply is insufficient and cellular fermentations come into play setting up autolysis or tissue degradation; from fats, new heterogeneous acid bodies are produced and from proteins, acid bodies are produced. In normal circumstances he considers that the amino bodies react with the new heterogeneous acid bodies and the resulting ammonium salts are converted the body into urea.

This explains the occurrence of Acetonuria in starvation without Acetonuric Acidosis.

In proof of Schoeniger's statements we may quote Von Noorden with regard to the relative amount of N which is excreted as Ammonia in Acetonuria.

Normally only the greater part of the Cellular Nitrogen is in the form of Urea, only 3-5% appearing as Ammonia. Von Noorden states that the Ammonia appearing in the urine is used to supplement the Potash Soda and hence salts which are lacking in the food and set free in Metabolism, in uniting with the mineral acids formed as a result of protein decomposition.
Acidosis: Nitrogen Excretion.

The classic experiments in which administration of mineral acids was followed by great increase in the amount of nitrogen excreted as ammonia, and state that administration of Acetone Body has a like result.

Norwood also made the statement that on a carbohydrate-free diet, the decarboxylated and \( \alpha \)-ketobutyric acids which appear in the urine are also accompanied by a great increase in the amount of nitrogen which is excreted as ammonia; the percentage of ammonia to total nitrogen rising from 2 to 4% to as much as 20 - 30%.

If now in a case with Acetoneuria, but no signs of Acidosis, the hepatic cellular activity were interfered with, less highly oxidized products would result from fat metabolism and less Ammonia would be produced from protein Decomposition ie the greater part of the \( \beta \)-ketoacids produced would circulate unchecked in the blood as various acids would be established, as previously described, and the patient would show rapidly increasing symptoms of Acidosis.
Acidosis—Condition of Liver.

With reference to the influence of the liver, it may be well to consider here, the subject of Post-Anaesthetic Poisoning. It is now admitted that after the administration of anaesthetics, whether ether, chloroform or Ethyl Chloride, acetoneuria practically invariably occurs—Beets states that acetoneuria invariably occurs after both ether and chloroform administration; Telford and Falconer found acetoneuria almost invariably after both ether and chloroform and also after Ethyl Chloride; Abram still found acetoneuria in 64% of cases. Becker and Hoch in 38% of cases also obtained similar results.

We also know that while very prolonged chloroform administration may only cause transient slight acetoneuria, the post-anaesthetic poisoning may follow the administration of a very small dose of chloroform.

The condition of the liver, post-anaesthetic poisoning with its anaesthetic poisoning is one of advanced fatty change. Fatty necrosis, that is in several cases, recorded...
Acidosis - Condition of Liver.

by Scheuer and Ballin. In the post mortem
appearances were more of acute yellow
atrophy. Anyhow in all the recorded cases
the post mortem appearances have shown
that the liver was not in a condition
to carry on its functions.

Scheuer believes that the liver is frequently
fatty in all cases in which post-
anaesthetic poisoning occurs and I
think we are at least justified in
concluding that in all these cases
its hepatic cellular activity was very
much interfered with before the cell-
renunciation of the anaesthetic so much
so that the anaesthetic effect of the an-
anaesthetic was responsible as to the
hepatic cells was sufficient to throw
the liver quite out of gear.

I think we are justified in concluding
that the condition of the liver in
cases which develop were in these
symptoms of acidosis is in most
cases a fatty change.

A great many of the patients who
develop acidosis are the subjects of
infective nutrition, some cases of
Acidosis: Condition of Liver.

Diabetic Mellitus. Cases requiring an operation under an anesthetic, and cases with gastric intestinal disturbance, for example. Noe Von Nooden 31 states that in cases in which a degree of insufficiency is present, the fat seeps into the blood to supply the organs requiring fat, thus justifying the deduction of Feldel who showed that in such conditions an enormous amount of fat passes from the subcutaneous tissue and abdomen and accumulates in the liver which may become 70% fat.

We may state therefore that in acidosis as opposed to simple ketonuria without symptoms of acidosis, the metabolism of fats is interfered with to a greater extent and in addition the hepatic cellular activity is so much lessened that the B chain butyric acid produced as a result of fatty fat metabolism is not neutralized and therefore produces symptoms of poisoning.
Cyclic Vomiting of Childhood:

This condition has only been recognized as a definite clinical entity within recent years but since its recognition and especially during the last ten years, many important papers have appeared on the subject.

The first examples of this condition reported in England were those described by Lee in 1882. He then described 8 cases, most of which appear, in the light of our present fuller knowledge, to have been true cases of Cyclic Vomiting—i.e., the patients were children and they were all subject to periodic attacks of vomiting with absolutely perfect health between the attacks. As will be seen later on, the liver plays an important part in these attacks and Lee evidently suspected some liver disturbance in his cases as he mention that during the attacks the stool were usually pale than normal.

The most important papers on this subject which have appeared since then are as follows:

In America, papers have been written by
Snow (1893) Ritch (1897) Rockford (1897)
Whitney (1898) Griffiths (1900) Keith Shaw (1902)
Picton (1903) Edsall (1903) Rockford (1904)
Moree (1905)
At Home: Hampstead (1905), Thane Veide (1905)
Mongan (1905), Reichardt (1903), Dickinson (1905)
Hampstead (1907)
In France: Mary (1899), Comby (1902), Rich-
reardt (1905)
All the above papers will be referred to later in great detail.

The clinical picture of Periostal Otitis
is a most striking one. The disease occurs
in children of all ages but is perhaps
specially common in children of six or eleven
years of age. Comby gave statistics of 34
cases and found that the majority of
cases occurred between 2 and 10 years of
age. He also found that of the 34 cases
he analysed, 26 occurred in girls and 10
in boys. These conclusions are fully borne
out by the cases observed in the out-pat-
tein Department of Paddington Green Chil-
dren's Hospital where the great majority of
cases occurred in girls. Comby stated that
Cyclical Vomiting: Symptoms.

There was usually distinct evidence of nervous heredity and that the cases occurred especially amongst the children of the richer classes. From the frequency with which cases of Cyclical Vomiting were observed at Paddington Green Children's Hospital it would appear that it is more common amongst the children of the poorer classes than has been generally supposed.

The disease consists in recurrent attacks of uncontrollable, and apparently causeless vomiting coming on at varying intervals sometimes every few months, sometimes every few weeks with apparently perfect health between the attacks.

Most frequently the attacks recur every 5 or 6 weeks and each attack lasts on the average about 3 days. Dickinson gives 2-5 days as the average duration of an attack and states that he has known an attack to persist as long as 3 weeks, but this is very unusual.

It is usually stated that the child
Cyclic Vomiting: Symptoms.

has been in perfect health before the attack began. On carefully questioning into the history we frequently find that for 12-24 hours before the commencement of the attack the child was either out-of-sorts, irritable, languid and sleepy, or the appetite was very poor for some days before; headache and constipation also frequently precede the attack.

With or without premonitory symptoms, the child is suddenly seized with uncontrollable vomiting which recur at intervals of 10-15 minutes usually. No preliminary nausea is observed. At first the contents of the stomach are ejected but latterly as the stomach becomes empty, the vomit is largely bilious probably from regurgitation of the contents of the duodenum. The child never complains of pain till towards the end of the attack when it may have some pain due to the act of retching with an empty stomach.

No attempt to eat is made during the attack but the child is always very thirsty and it is just as well to satisfy this craving even although it is vomited immediately.
Cyclic Vomiting: Symptoms.

As it gives the stomach something to complain upon.

While the attack lasts the child is extremely prostrated and lies in a drowsy apathetic condition, with the face pale and drawn and the eyes sunken.

The breath smells strongly of acetone, the urine is scanty and contains acetone and diacetic acid, usually in large amount.

In a rule acetone bodies are present in the urine at the beginning of the attack but may not appear till it is subsiding.

The temperature is almost invariably elevated. It does not usually rise above 100.4°F but in fatal cases which are extremely rare, the temperature may rise to a great height as in the fatal case recorded by Pangmead in which the temperature rose to 110°F before death.

The attack usually lasts for 2–3 days and the child recovers rapidly while it lasts.

Finally the vomiting ceases and it is most marvelous how rapidly recovery ensues. The child at once becomes quite bright and happy and though she had been...
Cyclic vomiting

only a few hours before, lying in a prostrated collapsed condition and vomiting continuously, she will now enjoy a hearty meal and keep it down too.

By the end of 48 hours or so after the cessation of the attack, the acetone bodies will have been found to have quite disappeared from the urine.

**Prognosis:**

The child may go on living thus for years, enjoying perfect health in the intervals between the attacks which always cease as the child approaches the age of puberty. It is certain that many of the so-called bilious attacks to which so many children are subject are really mild cases of cyclic vomiting.

So far only 7 fatal cases have been recorded, in 4 of which post-mortem examinations were performed. Of these Langmead has reported 3 and Pfeiffer 1. In all 4 cases the liver was buff or canary yellow — in fact a typical "fatty liver." Microscopic examination disclosed extreme fatty change in the liver cells.

In 2 of Langmead's 3 cases the kidneys also showed slight fatty change.
Vomiting.

In the case reported by Griffiths necrosis of the gastric intestinal mucosa was present which was thought to be primary but in hapman's cases no lesion of importance was found either in the stomach or in the intestines.

The following is a short account of a typical case of the condition:

Annie L. aged 4, admitted to Paddington Green Children's Hospital on August 29th, 1907 under the care of Dr. Rutinie.

For some days previously she had been very languid and off her food and the bowels had been very constipated.

On the afternoon of August 28th she was suddenly seized with frequent uncontrollable vomiting which continued at intervals for a few minutes until the admission; her mother stated that she had not complained of any feeling of nausea or pain and that the vomiting had become very violent after some hours.

On admission the child had a very exhausted appearance; the eyes were sunken and surrounded by dark rings and the lips were very languid and dehydrated. The tongue was dry and furred and the temperature was
Cyclic Vomiting: Illustrative Case

100°F. The heart and lungs were quite healthy and the liver was normal in size.

The breath had a very strong odour of acetone and the urine contained a very large amount of acetone and a trace of diacetic acid.

She was given a dose of calomel followed by a saline; the bowels acted well. The vomiting ceased, and next morning the child was quite recovered, quite bright and happy and eager for food.

After admission the acetoneuria gradually ceased and on morning of August 30th the diacetic acid had disappeared while the acetone was much less. On release the urine was quite normal and remained so during the remainder of her stay in hospital.

The previous history of the child was exceedingly typical; she had had similar attacks every 5 or 6 weeks for 18 months before admission; the attacks were gradually becoming more severe and were usually preceded by languor and want of appetite.

The child herself was of a very nervous hysterical temperament and the mother was an extremely neurotic woman.
The child was sent home a few days after the cessation of attacks and remained quiet for some weeks.
Then on November 22nd she was again admitted with a history of premonitory languor, headache, want of appetite and constipation for some days, followed by fever and vomiting. The mother noticed a peculiar smell of the breath before bringing the child up to the hospital. These attacks were similar to the one above recorded but also quickly passed off.

**Cause and Nature of Cyclic Vomiting:**
A great many theories have been put forward to explain the occurrence of these attacks, but the earlier theories have been all more or less discarded. I shall mention them however as many of them contain useful hints.

38. **Snow** regarded the disease as a gastric affection due to hyperacidity and absorption of jutamines.

39. **Combe** and **Peckford** & **Withey** considered that the attacks were merely manif -
Cyclic Vomiting: Cause.

- Reactions of the hereditary arthritis diar-thies. Comby also laid stress on the hered-
- itary nervous element in these cases and
- instances a few cases reported by Rockford
- in the Archives of Paediatrics for 1897
- in which attacks of cyclic vomiting in early
- life were replaced by migraine later in life.

Rockford and Whitney thought that the disease
- was a liothromic gastric neurosis due to the
- accumulation in the circulation of diffus-
- ible and poisonous leucocytes closely
- allied to the porrin bodies.

Richardson laid stress on the probable in-
- fluence of hepatic insufficiency in pro-
- ducing the attacks and stated that in
- cases of Recurrent Vomiting he had freq-
- uently observed signs of hepatic disarrange-
- ment in the shape of slight jaundice,
- enlargement or tenderness of the liver, pale
- stool, or bile-stained urine.

Piliquiti also believes that the attacks are caused
- by hepatic inadequacy. He believes that
- normally toxins are formed in system
- which are modified by liver before being
- eliminated by liver. If liver is out of order or if
- an abnormal quantity of toxins be elaborated.
Cyclic Vomiting: Cause.

...of...t...e circulation and cause a toxemia which may show itself as altered...phenomena, or recurrent vomiting.

Brock gave an account of five cases which accompanied Recurrent Vomiting but in which the attacks of vomiting ceased entirely after the removal of a chronically inflamed appendix. These cases are interesting and warn us to be on our guard in diagnosing Recurrent Vomiting but have no real bearing on the question of the causation of Recurrent Vomiting. Many thought that all attacks were due to constipation.

All the above theories regarding the causation of Recurrent Vomiting have now been discarded in favour of the view first enunciated by Edsall in 1908. He stated that Recurrent Vomiting is simply an acid intoxication of a type very similar to that found in Diabetes Mellitus and Post-Anaesthetic Poisoning. This view has now gained general acceptance and there is a very strong body of evidence in its favour. During the attack...
Cyclic Vomiting: Cause.

In the attack the child excretes large quantities of chloremic acid and acetone in the breath and urine and presents symptoms of chloremic poisoning combined with uncontrollable vomiting which, as we shall see later, resemble very much the symptoms observed in many cases of post-anesthetic poisoning. In the few cases also in which post-mortem examinations have been performed, the post-mortem appearances were identical with those observed in post-anesthetic poisoning.

Post-anesthetic Poisoning has now been proved to be a form of acid poisoning and we are therefore I think justified in including Recurrent vomiting in the same category.

Before dismissing the earlier theories we ought to take due notice of several important points which are therein referred to; these are (1) the frequency of nervous heredity and personal neurosis in the subjects of Recurrent Vomiting.

(2) the frequency with which the attack is preceded by constipation;

(3) the probability that the hepatic function....
Cyclic Vomiting: Production of Attack.

are defective; and (4) the possibility of an acute intoxication being present.

These few points are most helpful when one attempts to explain the exact mechanism of production of an attack which may be described somewhat as follows; following on constipation, toxins probably allied to uric acid bodies are absorbed from the bowel. These toxins so diminish metabolic activity especially in the liver that the fats are not metabolised sufficiently with the result that a large amount of 3-

hydroxybutyric acid circulates in the blood and cause symptoms of acid poisoning. The action of the hydroxybutyric acid is quite un-

checked because as a result of deficient metabolism insufficient ammonia base are produced to neutralize the acid bodies.

When we consider the definite neuropathic tendencies of children who are subject to this condition and the markedly periodic nature of the attacks it is even probable that the nervous system has a good deal to do with the production of the attacks. It is possible that where the attacks are precipitated by constipation the action on the liver take
Cyclic vomiting: Treatment.

Place through the nervous system and that where there has been no preceding contributition, the disturbance of the head may be purely nervous in origin.

The treatment of recurrent vomiting is unsatisfactory.

We must attend to the general hygiene and eliminate as far as possible all causes of excitement and worry; so that the child lives a healthy open air life and that the diet is a full easily digested.

As the post-mortem condition of the brain has shown that an important factor in the causation of attacks consists in the pericardial variability of the brain to metabolic fatty material, it is obvious that we should at least restrict the fatty elements of the diet. The avoidance of constipation is also obviously very important.

By means such as these, we may materially lessen the frequency and severity of the attacks but cannot hope entirely to cure the condition.

As to the actual treatment of an attack we can only, as a rule, adopt palliative
Cyclic Vomiting: Treatment.

Measures combined with some form of alkali treatment as recommended especially by Edeale. We must keep the child in bed in a quiet room, relieve the excessive thirst which is always present. In an attack of average duration we need not trouble to try to feed the child, but if the attack is longer continued it may be necessary to resort to rectal feeding. Nourishment by the mouth is quite hopeless during the continuance of the attack.

Edeale claims to have materially diminished the severity of the attacks by the use of different alkali in large doses. He gives about 100 grams of sodium bicarbonate or citrate as soon as symptoms manifest themselves and continues the administration till the child quite recovers from the attack. He claims that the urine should be rendered alkaline if possible.

Pisani states that he has aborted attacks of recurrent vomiting by giving large doses of different alkali sodium bicarbonate in what he considered to be the
Cyclic Vomiting: Treatment.

Prodromal period.

Marfan advocated injections of morphine during the attack and alkalies combined with sodium bromide. He claims that by this means the attacks were shortened and rendered less frequent and less severe.
Post-Anaesthetic Acidosis:

It has long been recognised that after the administration of an anaesthetic, a condition characterised by vomiting and delirium or coma may follow, and that this condition frequently proves fatal. In 1850 Casper in Germany expressed the idea that fatal chronic poisoning following the administration of chloroform does occur. Hale on many cases of post-chloroform poisoning were recorded in Germany and many experiments were performed to ascertain the effect of chloroform administration in animals.

Frittag summed up the results of repeated chloroform administration in animals as follows—fatty infiltration of the liver, cardiac and skeletal muscles and kidneys. He considered that the fatty changes were due to the action of the chloroform on the blood and tissue cells and that death was due to cardiac failure. Some individuals showed a much greater susceptibility to chloroform than others. During the past ten years or so
Post-Anaesthetic Acidosis:

These results have been confirmed by Heinzig, Bönder and Schenk. They also examined the livers of animals at the beginning of chloroform administration and several days afterwards and found on the second examination that the organs showed fatty changes — by varying the time of the second examination of the livers they found that the fat appeared several hours after the administration of the anaesthetic but did not disappear for days or weeks.

Within recent years Stiles and Macdonald have confirmed these results. They compared sections of liver removed before and after chloroform anaesthesia and found that, while the former were normal, the latter showed extreme fatty change.

They also found that when ether was used, the fatty changes were much lighter than after chloroform had been administered. The above experiments prove conclusively that the administration of chloroform can in animals at least produce fatty change in the organs and muscles generally but especially in the liver. Moreover, these fatty changes are identical with those which are
found post-mortem in Recurrent Vomiting and, as we shall later, in post-anesthetic acidosis also.

The first paper which appeared in England on this subject was that written by Sir Leonard Beetice in 1894 in which he described 9 cases of post-anesthetic acidosis; in 1903 he recorded 4 more cases.

In 1904, Tiele and Macdonald described several fatal cases and in the same year another important paper by Blanchet 29. 0 attends appeared; they described fatal cases of typical post-anesthetic acidosis following etherisation and were also the first to recognise that the symptoms of post-anesthetic poisoning are simply those of severe Acidosis.

In 1908, Kelly recorded a series of cases and expressed the view that some 'tumours' was at work interfering with metabolism and thus precipitating the attack. In the same year Hillard also described a series of cases and recognised that the symptoms were due to fatty acid poisoning. He also emphasised the frequency of tetanus in cases.
Post-Anaesthetic Acidosis:

Anaestheticisation added the gravity of the prognosis in cases with marked symptoms of poisoning.

In 1906, Seford and Buchanan recorded a case of acidosis following the administration of Chloral hydrate.

In 1907, Liebmund recorded a case of acidosis following the administration of nitrous oxide which recovered on careful clearing out of the bowel by means of enemas. The child was a specially predisposed subject as she suffered from Recurrent Vomiting but the case was nevertheless definitely one of post anaesthetic poisoning.

Description of the Attack:

Apart from the fact that delirium is frequently present, the symptoms and signs of post anaesthetic acidosis are extremely like those of an aggravated case of Recurrent Vomiting.

After recovering from the anaesthesia the patient usually goes on quite well till 12-36 hours have elapsed. Then ensues increasing languor or restlessness culminating in sudden wild deli-
Post-Anaesthetic Acidosis—Symptoms

Irritability. The pupils are dilated, and the expression anxious, and the patient loses
about in bed regardless of sheets or
dressings and blinks piercing screams at
intervals. The delirium frequently altern-
ates with periods of apathy or drowsiness;
the patient usually answers quite ration-
ally when addressed.

Vomiting is intense and vomiting is early
frequent and constant; at first the vomit
is Watery and bilious but eventually becomes
coffee-ground from admixture with blood.
Bleeding can be smelled in the breath and Reek
acid usually diarrhea and are present in
the urine.

The temperature is not usually much ele-
crated but in a fatal case may rise to
105°F or higher before death.

Emaciation is very rapid and the eyes
quickly become sunken and the face hagg-
ard.

In many cases the delirium quickly subsides
and consciousness descends into coma which
ends in death. In some cases death oc-
curs from heart failure during the stage
of acute excitement.
Post-Anaesthetic Acidosis - Illustrative Case.

It is not uncommon to get slight delirium and rather troublesome vomiting following the administration of an anaesthetic but the fully developed cases are very rare.

The description of an illustrative case which occurred recently at Paddington Green Children's Hospital, follows —

Eva Knight, aged 6 years 10 months. Admitted Nov. 16, 1907. Disease — Incurable Disease of Hip.

Previous History: subject to attacks of what were evidently periodic vomiting, from the age of 3½ years. As first the attacks were frequent and severe but gradually diminished in frequency and severity and almost ceased for some time before admission. Had a very slight attack only lasting a few hours in the beginning of October 1907.

Following an operation in 1905 the child had very severe vomiting which continued for 2 days.

On admission the child's condition was fairly good and the heart and lungs were healthy.

On Nov. 18, 1907 the great trochanters was excised and tuberous tissue removed. The child remained fairly well for twelve hours after the operation but then became very unconscious.
and vomited twice.

On the 19th of November the child continued very aqeuous and did not vomit and was very languid and apathetic and the temperature on the evening of the 20th rose to 102.2°F and the pulse to 136.

On the 21st the child showed slight general jaundice and in the evening the apathy changed rapidly to excitement and the child was very irritable and restless and towards midnight was wildly excited and quite delirious.

On the 22nd the breasts became atrophic, of lactation and vomiting became frequent. From this time onwards the child gradually sank and died in a state of coma of heart failure, early in the morning of the 26th.

A post-mortem examination was performed and the liver and kidney on both naked-eye and microscopic examination showed marked fatty change.

The case was evidently one of post-anesthetic acidosis in a child who was specially predisposed to it being already the subject of recurrent vomiting so that a condition of hepatic inadequacy was prob-
The Post-mortem appearances are very fully and clearly described by Guthrie. They are identical with those found in Recurrent Vomiting and he states that they are almost invariably present: the condition being one of advanced fatty change in the liver both on naked-eye and microscopic examination.

It will be observed that Guthrie states that these appearances are almost invariable: he does so because in ten or twelve cases recorded by Schmick and Ballin, the appearances were those of Acute Yellow Atrophy.

In any case we are justified in saying that the post-mortem appearances show the liver to have been in such a condition as to render its proper functioning quite out of the question.
Nature of Post Anaesthetic Poisoning:

As I have already stated, Brereton, Storey and Poore were the first to state that Post Anaesthetic Poisoning is simply Acute Acid Poisoning (vide p. 55 infra). This has been adopted since then in all the important papers which have appeared on the subject.

I have already fully gone into the question of post-anaesthetic acetonaemia and have shown that transient acute acetonaemia invariably follows the administration of chloroform, ether or ethyl chloride (vide supra p. 34).

I have already shown that the appearance of acetone bodies in the urine indicates a disturbance of fat metabolism and we are therefore justified in concluding that the administration of ether, ether in chloroform cause a degree of interference with metabolism in almost every case.

Now we know that the liver is a most important seat of fat metabolism and that the condition of the liver in fatal cases of post-anaesthetic poisoning is
Post-Anaesthetic Acidosis: Nature.

One of advanced fatty change.

The clinical picture of the condition is very similar to that of recurrent vomiting and the patient excretes large quantities of acetone and diuretic acid by the breath and urine.

We are justified, therefore, in concluding that the condition is one of severe acidosis, the toxic agent being probably butyric acid.

On referring again to pp. 34 and 35, further arguments will be found adduced in favour of the view that the liver is adversely functioning badly in cases where there is Post-Anaesthetic Acidosis, and that this diminution of hepatic activity is probably very frequently due to an excessive deposit of fat in the liver cells.

I may adduce several additional points here which are in favour of a previous ly existing fatty condition of the liver — in the experiments performed by Steel and MacDonald very large doses of chloroform were given. Considering the size of the animal experimented on and though in these cases extreme
fatty changes were produced in a previously healthy liver, it seems very unlikely that since a small dose of anaesthetic as is administered in the course of a surgical operation could produce such an advanced fatty change if the liver were previously healthy.

In addition Hills and Macdonald showed that inhalation or subcutaneous administration of ether produced little or no fatty change in the liver and yet in fatal cases of acidosis, following administration we found just as advanced fatty change in the liver, as in post chloroform acidosis.

In the case of post anaesthetic acidosis, which I have just described (vide p. 53) the child had previously undergone an operation which was followed by vomiting which was recovered from. And in many cases it is found that the patient had previously undergone an operation without any recurrence present, it seems likely then that in the latter case, there must have been a new factor at work causing the development of acidosis.
In Eva Knight's case (p. 58) and in Langmead's case (p. 56) the child had previously been subject to recurrent vomiting for years, a fact which almost entitles us to suppose a previous existing fatty condition of the liver.

Langmead's case is especially interesting as the anaesthetic itself was nitrous oxide, and the acidosis resulting was typical post-anaesthetic acidosis of a fairly severe type, and it seems out of the question to suppose that the short anaesthesia which is obtained with nitrous oxide could cause such a marked derangement of fat metabolism unless the liver had previously been functioning badly.

Anyhow we are justified in concluding that the liver was previously functioning badly in cases which develop post-anaesthetic acidosis, and there are many points in favour of its previous condition being a fatty one.

Still, there were several points which
in many of the cases, subject either acute
or chronic, was present and thus of course
in a well-known cause of fatty change
Post Anaesthetic Acidosis:

A great many cases requiring operation show a greater or less degree of emaciation and, as stated already (vide p. 316), in conditions of emaciation the liver cells tend to be very largely filled up with fat.

Treatment of Post Anaesthetic Acidosis:

The way to do a good deal in the way of preventive treatment but once the condition is fully established we can do really very little indeed.

Preventive Treatment

Delay operation if possible in cases where fatty liver is suspected such as cases of sleep apnoea, diabetes mellitus or cases in which there is a history of previous attacks of recurrent vomiting; during the period of delay prepare the patient by careful attention to secretory functions and by the administration of sodium bicarbonate or citrate, as recommended by Breed.\(^{25}\) In order to neutralise any existing fatty acids also pay careful attention to the diet restricting especially the amount of fatty
material.
If the patient is the subject of recurrent vomiting, the safest time to operate is shortly after the attack, as soon as the child has regained normal health. Seldrow and Halstron record two cases of this sort and in both the anaesthetic was administered without any untoward result.

True elevation causes acute acidosis, it would be advisable to give a nutritive  
evening two hours before the operation and another immediately after.

Fasting in all cases in which a fatty  
lining is injected, we should give eters  
instead of chloroform, as long as ether is  
not very well contraindicated. This practice  
is followed I believe in Mr. Steel's  
wards in the Edinburgh Hospital for  
Sick Children.

The treatment of the actual attack of  
Post Anaesthetic Poisoning is very unsatisfactory — almost all fully developed  
cases end fatally.

We must do all we can to get the bowel to act, and must work out the bowel  
with large enemata which will get red
of any effete products in the bowel. The effort to combat the acid intoxication is usually of little avail, but we may try subcutaneous injection of large quantities of sodium bicarbonate solution, 1/2 in. of a pint of saline solution, the injections being made in the sub-mammary or axillary regions or in the flanks. Intravenous infusion of large quantities of normal saline solution will also serve to dilute the poison circulating in the blood. Beyond this, we can do no more than to keep up the strength by every means in our power; nutrient enemas will frequently be found necessary on account of the vomiting.
Salicylate Poisoning:

This condition is rare, and has only appeared in its full degree when heroic doses of sodium salicylate were being given in a patient who is getting very large doses of sodium salicylate every day. Observe gradually deepening drooping which may or may not be accompanied by vomiting. The child is flushed and the eyes are bright and red. Humps of the Kussmaul type may be present while the drooping may be preceded by delirium. The breath smells strongly of acetone and the urine contains a large amount of acetone.

From the above description it will be evident that the clinical picture presented by the child is that of a typical case of Acidosis.

Dr. Hess in his Harvard lectures of 1903 advocated the use of large doses of sodium salicylate in acute rheumatism in children, from 100 to 200 grains, with his usual dosage.
Salicylate Poisoning

In children aged from six to ten years, he mentioned that in one case symptoms similar to diabetic coma supervened. Evidently this was a case of toxic salicylate poisoning by sodium salicylate. This case is also mentioned by Raymead in his paper on the subject; he also gives details of seven other cases which were under treatment for acute rheumatism with large doses of sodium salicylate. All the cases presented typical symptoms of salicylate poisoning and had acetone in the breath and urine. In one case examined by a special process acetic acid was also detected in the urine. A special process is necessary in these cases because of the presence of a salicyluric compound in the urine which interferes with the reaction given by the ferric chloride test. Two of the cases died but the report of post-mortem examination was minute unsatisfactory; the lungs, kidneys and brain were said to be normal but the liver was not mentioned. Raymead concludes therefore that in children sodium salicylate if given
Salicylate Poisoning

In large doses may cause symptoms resembling the acid poisoning of Diabetes. The adrenes therefore that the Sodium Salicylate should be omitted when acetoneuria appears or when the urine becomes more and more acid, also that the excretory functions should be kept in active working order and that alkali may be given along with the Sodium Salicylate.

Treatment:
Preventive. Always give sodium bicarbonate along with Sodium Salicylate if large doses are being given. Keep the bowels open and the urine alkaline.

If acid poisoning occurs, we simply apply the treatment already advised for post-anæsthetic Poisoning namely, lumina alkalies, saline transfusion or subcutaneous infusion of Sodium Bicarbonate solution.
Acidosis in Diabetes Mellitus:

It is now an admitted fact that diabetic coma is merely a form of acidosis. I shall therefore say no more concerning the condition than is necessary to bring it into line with the other forms of acidosis.

Other gives an admirable review of the subject in his System of Medicine and refers to the investigations by Stadeleman, Kugl, and Windowski which proved that the symptoms were due to the circulation in the blood of fatty acids.

We have already shown that the acid results from grave interference with fat metabolism. Clinical observation has shown that the most frequent cause of the suicide of diabetic coma are precisely those which are instrumental in interfering with the metabolism of fats, the more frequent precursors being perhaps, overintoxication or too complete abstinence from the carbohydrate elements of diet.

Other divides the cases of diabetic coma into three great groups according to symptoms:

1. Drowsiness, deepening into coma and death.
Diabetic Coma:

2. Cases which begin with preliminary gastric disturbance or with some local complication such as suppuration. These cases may begin with delirium and air hunger and gradually sink into coma, ending in death.

3. Sudden headache and feeling of intoxication deepening rapidly into fatal coma.

The breath usually smells of acetone in Diabetic Coma, and the urine contains large quantities of acetone and diacetic acid.

Post-mortem, the lungs frequently show advanced fatty change.

It is evident therefore that Diabetic Coma is simply a form of Acidosis and the treatment should therefore be the same as that laid down for the other forms of Acidosis. But this case is fully developed however, it always ends fatally, though in many cases the subcutaneous infusion of sodium bicarbonate solution may effect a temporary return to consciousness.
Pericious Nausea of Pregnancy:

While admitting that in many cases the Nausea of Pregnancy is quite evidently due to mechanical or nervous causes, still a certain proportion of severe cases remain in which, as Langdon Brown has observed, there is a toxæmia of some sort present. There are several points in favour of the view that this toxæmia may be due to an acid poisoning, the abnormal acid being probably elaborated from imperfect fat metabolism.

Thus Whitridge Williams found that in a case of Pericious Nausea of Pregnancy, the nitrogen excretion remained at the normal level but the percentage of nitro-oxide excreted as ammonia was very largely increased. As I have already pointed out (vide pp. 32, 33) this is very strongly in favour both of the attempt to neutralise an excess of acids in the system and also of a defective hepatic activity. Whitridge Williams also expressed the opinion that a certain number of cases of Pericious Nausea were due to acid poisoning.
an illustrative case has recently
been published by Dr. Helen Baldwin
which strongly supports this view.
The case was one in which a patient
suffering from Persistent Vomiting
of Pregnancy was reduced to previous
a condition that the induction of
labour was determined upon.
Before induction, in addition to proin-
cub-vomiting, it was found that
the urine contained both Acetone
and Diacetic Acid; after induction
of labour the acetonuria gradually
diminished.
On the 10th day after induction labour,
a relapse occurred; the patient com-
plained of nausea and headache
and again began vomiting. On ex-
amination of the urine it was again
found to contain a large amount
of Acetone and Diacetic Acid.
Suitable treatment was adopted and
was followed by an uninterrupted recovery.
The whole subject requires further
investigation but I think we are
justified in concluding that some
Pernicious Vomiting of Pregnancy:

of the severe cases of Pernicious Vomiting of Pregnancy may be due
to acid poisoning.

As to the causal factor in the
interference with fat metabolism
nothing definite can be said at
present. It is evident however, that
a woman who is pregnant and
has therefore an extra strain thrown
on her metabolic processes, is pec-
uliarly liable to have these processes
thrown out of gear. It is possible
too that the pressure of the preg-
nant uterus on the bowel, interfering
the normal onward passage of the
intestinal contents and thus facilitating
the absorption of toxic products from
the bowel, may afford an explana-
cation of the toxemia which is prob-
ably the cause of the break down of
metabolism.
Acidosis due to Gastro-Intestinal Disturbance:

I have already pointed out (p. 73) that acetonuria is frequently due to gastro-intestinal disturbance and that many of these cases, if carefully examined, show also slight symptoms of Acidosis; on page 28 of this volume I described a typical case of this nature.

Two illustrative examples may prove of interest:

1) A boy of 8 was admitted to Paddington Green Children's Hospital on Sept. 16, 1907 under the care of Dr. Guthrie. Two days before admission he had partaken heartily of luncheon and shortly after he became very drowsy and began to vomit and continued vomiting frequently; the bowels were not opened.

On admission the boy was very restless and drowsy and complained of headache; the temperature was 100° F.; the breath smelt strongly of acetone and the urine contained a large amount of acetone and diacetic acid. Under mealtimes and exercise the symptoms gradually disappeared and coinci
Paedro-Intestinal Acidosis:

...dently with the disappearance of symptoms the acetonuria disappeared.

The boy had never had any previous attacks of this sort. But had always been very constipated.

The case was obviously one of acute-acidosis; the liver was probably already functioning badly as a result of the existing constipation and broke down in the attempt to deal with the large amount of fat supplied in the meal of liver and bacon.

2. Boy aged five years admitted to Paddington Green Children's Hospital on September 27, 1907 under the care of Dr. Guthrie.

For some days before admission had been languid and had no appetite; the lips and feet had been slightly swollen.

On admission the child was very languid, the temperature was slightly elevated and the feet and legs were slightly oedematous. The stools were
Gastro-Intestinal Acidosis.

The urine contained a good deal of acetone but no albumin. For four days after admission the child continued to improve and the acetone became much less. Then came a relapse, the stool became very offensive and continued so in spite of careful regulation of the diet and aperients and intestinal antiseptics combined with washing out of the bowel. The temperature again rose and continued raised and irregular till the end; the drowsiness gradually increased and the oedema gradually became general. Acetone and glucose reappeared in the urine and were both present in large amount before death. The drowsiness deepened into coma in which condition the child died about one week after admission.

A post-mortem examination was performed, the lungs were extremely fatty and the kidneys also showed slight fatty change. This was confirmed by...
Gastro-Intestinal Acidosis:

Microscopical examination and no sign of nephritis could be found. The case was evidently a severe form of acidosis the kidney functions having been interfered with as a result of absorption of toxins from the bowel.

As nephritis was excluded, the general oedema was probably associated with the gastro-intestinal disturbance, a class of case which sometimes occurs in children.
Conclusions:

1. That Neale's Test and the Liquor Ammonia Test are the two best clinical Tests we possess for Acetone; that both are sufficiently delicate, but that, if anything, Neale's Test is preferable both for delicacy and freedom from fallacy.

2. That Acetonuria is very common in children and that the Acetone Bodies are usually present in large amount in these cases.

3. That the main causes of Acetonuria are 1. Poisoning whether due to intoxication or Drugs or Organised Necrosis and 2. Deficient oxidation of the Tissues.

4. That Acetonuria almost invariably results from the administration of Ether or Chloroform.

5. That the main source of Acetone Bodies is Fat.

6. That the Carbohydrates aid fat metabolism through the oxygen which they contain.

7. That Acidosis or Acid Poisoning is the condition resulting from the
Conclusions:

1. Unenhanced circulation of keto-acidic acid which in turn results from very deficient metabolism of fats.

2. That the cardinal symptoms of Acidosis are three in number, viz. stupor, going into coma, delirium, and vomiting.

9. That slight degrees of Acidosis are common in children especially as a result of gastro-intestinal disturbance.

10. That, once a condition of Acidosis is fully established, the prognosis is practically hopeless, except in Cyclic Vomiting.

11. That, to allow of the development of symptoms of Acidosis, the hepatic functions must be defective.

12. That the most important forms of Acidosis are Cyclic Vomiting, Post Anaesthetic Poisoning, Salicylate Poisoning, Diabetic Coma, and some of the severer cases of Pernicious Vomiting of Pregnancy.

13. That the typical post-mortem condition present in Acidosis is marked
Conclusions:

fatty change in the liver.

14. That there is a strong nervous influence present in cyclic vomiting and that the exciting cause of an attack is frequently some bowel disturbance.

15. That general hygiene and diet are important in treating cyclic vomiting and that during the attack the treatment must be mainly eliminant combined with an attempt to neutralize the acid poisoning.

16. That well marked Post-Anesthetic Poisoning is almost invariably fatal.

17. That in all probability the majority of cases of Post-Anesthetic Poisoning have a fatty liver previous to the occurrence of Acidosis.

18. That, in cases where a fatty liver is suspected, ether should always where possible, be used in preference to chloroform.

19. That the treatment of Post-Anesthetic Poisoning should be dir-
Conclusions:

...tend towards neutralizing and diluting the circulating poison.
Bibliography:

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Bibliography.

32. See "Fitful or Recurrent Vomiting" St. Barnabas Hospital Reports. 1882 p. 1.
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