A Thesis

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by

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Diaceturia and Acetonuria

with special reference to the effects upon children

of the administration

of

General Anaesthetics
Diabetic acid is not present in normal urine; but under certain conditions of metabolism, it is present in urine and blood. We may distinguish between cases in which the acetone bodies, β-oxybutyric acid, diacetic acid, and acetone are simply present in the urine—the condition of so-called "acidosis"; and cases in which we have, added to their presence, the symptoms of acid intoxication.

Noteworthy, records that Hanlich first called attention, in 1846, to the presence of acetone in the urine; in diseases of the stomach and intestines. Bastin, in 1865, confirmed this; and, since that time, much work has been done with regard to acidosis.

The conditions in which acetonemia is met with, were classified by von Jahrech as follows:

1. Acetonemia due to gastrointestinal disorders; such as appendicitis, enteritis, intestinal obstruction, epidemic diarrhoea, and gastric ulceration.
3. Acetonuria associated with the presence in the body of specific organisms e.g. pneumonia and diphtheria.
4. Acetonuria due to the viability of the body to use up carbohydrates - as in Diabetes. Emaciation and cachexia of malignant disease.
5. Acetonuria due to the action upon the body of poisons such as phosphorous, salicylic acid, and general anaesthetics.

Asler and Melboue define "Acetosis" as the disturbance that results from the predominance of acids in metabolism. They give the chief sources of the acids that may be present in the body, and which may be excreted in the urine; as the acids of carbohydrate fermentation in the alimentary canal.

1. Sulphuric and phosphoric acids derived from metabolism of common protein and nuclein.
2. Malonic Acid
3. Members of the Acetone group - Diacetic Acid and Byrobutyric acids.
5 Other acids in the body
glyceronic, uric, oxalic etc.

To neutralise the last group we have the
alkalies in a mixed diet, and in water
If the alkalies are deficient, the acids
are neutralised by the fixed alkaline of
the body, and the ammonia of Metabolism.
Therefore, a deficiency of alkalies, or
an excess of acid, sets up Acidosis.

The acids of group I are easily oxidized

The constitution of Lactic Acid is similar to
that of Alanine; a derivative of protein
by hydrolysis, and lactic acid may be
derived from protein or from carbohydrate.
It is not thought to be important as a
cause of Acidosis.

The symptoms produced by acidosis are
variously explained as being due to
1. Acridity
2. Nation withdrawal leading to
protoplasmic disintegration.
3. Toxicity per se - lack of oxidation
With regard to these suggested causes the author points out:
1. That the acidity of the blood has not yet been proven
2. That some cases of Acidosis occur with no previous withdrawal of Natrium

In discussing the origin of diacetic acid and acetoone it would be well to first consider the chemistry of these bodies.

Diacetic Acid has the formula: $C_4H_6O_3$
In being heated to boiling point it splits up into acetone and carbon dioxide:

$$C_4H_6O_3 \rightarrow CH_3COCH_3 + CO_2$$

It is not present in normal urine; it always accompanies oxy butyric acid; but it may be present apart from this acid. Dickson Mann says that it rapidly disappears from urine which is left to stand; and that the urine should therefore be tested as fresh a condition as possible. The usual test employed for its detection is urine
is the Feric Chloride test.
To an inch of the urine to be tested is added a little of a solution of Feric chloride. If diuretic acid be present, the urine becomes a deep red tint, resembling that of claret and water very often; a white cloud forms on adding the reagent. This is due to the formation of feric phosphate; and is dissolved by adding excess of the reagent.

When the solution is boiled, the coloration becomes less distinct and may disappear. A fallacy is apt to occur in testing the urine of patients who have been taking certain drugs viz. salicylates, phenacetin, salol, aspirin, diuretics and aspirin, as the urine of these patients gives a rather similar colour.

When such urine is tested, there is no reduction in the coloration.

Another test, which is useful to confirm the above is Priezger's Test— which is performed as follows.

To 10 c.c. of urine, add 3 c.c. of 10% solution of iodine acid, and 3 c.c. of chloroform. Shake the solution.
If diacetic acid be present, the chloroform remains colourless; if absent, the chloroform is coloured rose red.

Pigler's test is unaffected by the presence of salicylates, aspirin, etc.

If the urine be very dilute we may still get the chloroform remaining colourless, because the iodine acid is not reduced.

To avoid this, we can take 2 c.c. of normal urine; and add to it 2 c.c. of iodine acid solution.

Add 3 c.c. of chloroform and shake. The chloroform becomes coloured.

Then add 10 c.c. of the urine to be tested and shake well.

If diacetic acid be present it finds the iodine which is formed from the iodine acid by urea and other normal constituents of the urine, and so the chloroform becomes colourless again.

Acetone is dimethyl ketone $\text{C}_3\text{H}_6\text{O}$. It is present in normal urine in traces; not more than 0.01 gms in 24 hours, according to Von Galsch.
It is produced during the breaking down of mono-amino fatty acids in the absence of an adequate amount of carbohydrate material.

The test which I have used for the detection of acetone in urine is Leibniz's Test using the urine itself, proceeding as follows.

1. 5 c.c. of a solution of caustic potash, drop in aqueous solution of iodine in potassium iodide until a faint yellow coloration is permanent.
2. Then, by means of a pipette, float carefully a few c.c. of the clear urine on to the iodine solution, so as to form a supernatant layer. A thin white disc of iodoform crystals appears in a few seconds if acetone is present.
3. The disc is examined microscopically for crystals of iodoform—which are usually hexagonal crystals of faint yellow color. They may be in the form of needles; or may be stellar crystals.
4. Acetone may be present in urine which does not contain diacetic acid; due to the latter having been decomposed.
The three acetone bodies form a series

$\beta$-oxybutyric acid $\quad$ $\text{C}_4\text{H}_6\text{O}_3$

Diaetic acid $\quad$ $\text{C}_4\text{H}_6\text{O}_3$

Acetone $\quad$ $\text{CH}_3\text{COCH}_3$

$\beta$-oxybutyric acid is easily decomposed by oxidation into Diaetic acid; and the latter is easily changed into Acetone. This is of importance in considering the origin of Acetone and Diaetic Acid.

It has been thought, at different times, that the Acetone bodies were formed from carbohydrates, from proteins, and from fats.

It has been proved, by feeding experiments, amongst others by Schuman declared, that Acetone is not produced from carbohydrates.

Lorenz thought that the appearance of Acetonuria does not justify us in drawing any other conclusion than that protein metabolism is low.

Oster and McVoa consider that Acetonuria could occur only very late in a protein free food; since
the protein metabolism is low.

It is agreed that the Acetone bodies can be formed from proteins to a limited extent, but the experimental work which has been done in recent years, points to the fat as being the chief source of these bodies.

Langdon Brown found that the excretion of acetone bodies is not accompanied by the excretion of nitrogen and sulphur in such quantities as would be the case if the acetone bodies were derived from protein only.

Butyric acid is formed by the action of bacteria on fats - this is easily changed to oxybutyric acid, which, by oxidation, becomes diacetic acid.

Schwyzer gave butter and sodium butyrate, and found an increase in the acetone excretion. The same experimenters also found that in healthy people fat causes only a minute increase of acetonuria, whilst in cases of severe diabetes, fat causes a distinct increase of acetonuria.
On the other hand, Blumenthal denies that the tissue fat can be converted into acetone; although he admits that the fat which is received into the stomach may be a source of acetone.

Geelmuideren, Hagenberg and Blumenthal all agree that fat of some form can cause an increase in acetone output. Schuman, Peckercy came to the conclusion, after experimenting upon himself, that the decomposition of fat is the most important cause of acetone excretion. An important point is, that oxylutynic acid, which is so easily changed into acetone can be formed from the decomposition of fats.

Porhardt thought that there existed in the protein molecule, two groups, which are concerned in the formation of the Acetone bodies.

1. The keto plastic group—which favours acetone formation.
2. The anti keto plastic group—which antagonises acetone formation.

The first group contains fats and the lower fatty acids.
The second group - anti-anabolic, contains carbohydrates and glycérine.

In diabetes there is an inability to use the carbohydrate food; and the amount of this inability determines the quantity of acetone in the blood and the urine. It may here be pointed out that, by some authorities, it is thought that the fats which are taken into the alimentary canal, are broken up in passing through the layers of the canal wall into fatty acids and glycérine; and that these bodies combine together again for the fat to be absorbed by the lacteals. If this were so - it might be a possible origin of oxybutyric acid and of acetone.

In connection with the origin of acetone bodies, it is well to consider the distribution, in the body, of Chloroform and Ether; after their administration. These anaesthetics are absorbed by the lungs and are carried all over the body by the blood. Both are found in larger quantities in the...
Brain rather than in the blood, liver and muscles—
which suggests that the fatty degeneration of
the liver seen in chloroform poisoning
is not due to the direct action of the
chloroform upon the liver substance.

Excretion of these anaesthetics takes place
mainly by the lungs.

Some of the chloroform inhaled seems
to undergo combustion in the body.\[18\]

Part found chlorides in the urine increased
after its inhalation. Hydrochloric acid
is formed by the combustion; and the
acidity of the urine is increased.

According to Osler and McPhee, acidosis is
produced by the administration of mineral acids,
and by the use of an acid and alkali-free
diet; acidosis is set up.

At autopsy on a patient who died from
chloroform during the administration of
the anaesthetics; Pororoshin found some
degeneration of the liver, kidneys and
heart. This would seem to prove
that such a condition can be brought
about very quickly; the patient having been
in apparently good health previous to the operation.

This is important, as it shows that delayed chloroform poisoning may also bring about a fatal ending in a few hours.

I lay emphasis upon the combustion of chloroform in the body; as it may be a cause of acidosis through causing diminished oxidation in the tissues. It also leads to acidity, and therefore a notion of deficiency, another cause of Acidosis.

B-oxalylacetic and Dicetic Acids represent the lower stages of the decomposition of 2. and are excreted as such either in consequence of diminished oxidation, or of excessive metabolism. Geiringer has experimented upon himself, and found that when he deprived himself of carbohydrates—much more acetone was excreted in the urine; so that the capacity of the organism to decompose dicetic acid is lowered by the absence of carbohydrates from the diet. The carbohydrates supply the oxygen for metabolism
and lack of carbohydrates leads to defective metabolism of fat in the tissues. The fat of the tissues is metabolised into carbon dioxide and water by oxidation. If oxidation be deficient, fatty acids are formed. These form oxybutyric acid which forms acetone. Therefore lack of carbohydrates, and the inability of the body to use the carbohydrates, cause this to take place.

This is the probable explanation of the presence of these acetone bodies in the blood and urine in cases of diabetes, and in emaciation and cachexias.

In cases where poisons are taken into the body there is probably an interference with carbohydrate metabolism; and so with fat metabolism which is dependent upon the former.

Another possibility is that they are oxygens formed from the carbohydrates which is necessary for the metabolism of fats.
It is, therefore, important to avoid a concentration of chloroform inhalation and it is advisable to combine the administration of oxygen with that of chloroform and also with that of ether, if given for any length of time.

In post-chloroform poisoning, we have also to deal with a deficiency of nutrition due to the acidity produced by the chloroform. Hence alkalies are indicated in the treatment of these cases.

Langdon Brown, writing in The Practitioner in 1907, on Acetonuria said, that if more than half a gramme of acetone is being secreted in a day, diacetic acid is certain to be found also. He found that carbohydrates diminish the quantity of acetone bodies in the urine in the circumstances that is frequently seen in the treatment of cases of diabetes.

That the Acetonuria of pelvic diseases could be largely inhibited by supplying the
wasting tissues with carbohydrates was proved by von Noorden in treating cases of Enteric fever.

The question that next arises is, given the formation of such acetone bodies — how is the state of "acid intoxication" produced? by which is meant the state of toxemia which is superadded to the presence of acetone bodies in the urine.

That these bodies can be present in the urine without giving rise to any ill effects is well known.

At the Manchester Children's Hospital I have examined the urine of 271 cases before and after operation. The details of these cases, with the analysis and deductions therefrom, are given below. Considering for the moment the presence of diacetic acid in the urine, I found the following:

The 271 cases were composed of:

- 237 non-septic cases
- 24 tuberculous cases
- 11 septic cases
Taking only the non-septic cases, which were admitted for operations which were not urgent, e.g., hernia, genu valgum &c., 13 patients, i.e., 4.7% had diacetic acid in the urine before operation — when they suffered from no ill effects from its presence in the body.

Fern, in an article on Acetonuria in Childhood, gave results of the examination of the urine of 66 cases, where 61.6% were found to contain acetone soon after admission. These, however, were medical cases, and in no way analogous to the series of surgical cases given above.

Ball, in 1903, examined 40 cases; without once finding diacetic acid before or after anaesthetic administration. He later examined a large number of cases at Guy's Hospital, with the same negative result.

On the other hand, Telford and Falconer found that out of 160 non-septic cases,
3% contained diacetic acid previous to the administration of an anaesthetic.

It is a fact that a child, in apparently good health who is admitted to hospital on account of some deformity which is required to be put right; may have diacetic acid in the urine; and be none the worse for it so long as no anaesthetic is given to the child. The acids themselves are not toxic, as has been proved by giving them to animals by the mouth and by hypodermic injection.

Origin of the Acetone Bodies

The origin of the acetone bodies is now agreed to be partly protein and chiefly fat. The cause of their formation would appear to depend upon defective oxidation. This deficient oxidation is brought about in different ways in various conditions.

1. In cases of poisons, such as phosphenes...
and chloroform,
it would appear that the liver is
acted upon either immediately, as
is thought by Beathe and Carmichael;
or after it is already a fatty liver, as
is held by Guthrie.
The liver is thrown out of action, and
cannot utilise the carbohydrates;
thus leading to deficient oxidation.

2. In cases of Emasculation,
it may be that the ammonia which is
normally formed from proteins is
deficient.
The acids, which are produced by autolysis,
can thus throw the liver out of action —
producing the same results.

3. In Diabetes,
there is an inability to utilise the
carbohydrates — with like a effect.

4. In Septic cases,
The liver is again probably unable
to do its work properly.
A possible explanation of chloroform poisoning.

In chloroform poisoning, or to be more exact, delayed chloroform poisoning, two explanations are given as to why certain cases should be more affected than others.

Barrie and Beattie[27] think that there is an idiiosyncrasy of the subject, whilst Guthrie[28] holds that there exists already a fatty condition of the liver, and that the anaesthetic proves to be the last straw.

Against this latter view is the experiment performed by Northcote—and by Stiles and MacDonald[29] of excising a piece of the liver of an animal before and after the administration of an anaesthetic; when it was found that the fat in the liver was increased—the anaesthetic being chloroform.

A possible explanation of these cases of so-called idiiosyncrasy appears to me to be
the following.
Chloroform is inhaled.
A certain quantity requires oxidation.
In the majority of people this oxidation
takes place without any ill effect.
But, in some, depending upon the condition
as to metabolism, it leads to
defective oxidation of the tissues, so
that the fats are not properly
oxidized, and a condition of acidosis is
set up.
This condition of acidosis may not be
harmful — if the acetone bodies can
be got rid of easily (see number of
cases where diacetic acid is found after
anaesthetic administration, with no
bad effects).
But if they are not excreted properly
—and not chloroform death may
occur with no acetone bodies in urine
— then the liver is put out of gear;
and it becomes unable to utilize
the carbohydrates — thus leading to
a still greater deficiency of oxidation
and to a greater degree of acidosis.
The acidosis produces a Katin deficiency in the body, and this leads to protoplasmic deterioration—with poisoning of the body by some, at present unknown, substances; possibly of the nature of phomains.

These cause the symptoms of "fatty intoxication" and may cause the fatty condition of the liver, and other organs.

The "acidosis" is not the immediate cause of the symptoms; but the amount of acidosis is proportionate to—and therefore, an index of—the amount of intoxication.

The acidosis in the blood or acetonemia is the real index. If the acetone bodies are excreted well, there is no call made upon the Kations; and, therefore, no disintegration of the protein molecule of Borchardt.

This explains the fact mentioned above, that some cases may have diabetes and in the urine with no sign of intoxication.
Nor is the fatty condition of the liver a cause of the symptoms; except that it leads to further incompetence of the liver to use up carbohydrates. In all probability too much importance has been laid upon the changes which take place in the liver. Fatty changes have been found in the heart muscle, and kidneys. The jaundice sometimes seen in these cases may be due to the action of the anaesthetic upon the blood supply.

The condition of the pancreas has not, so far as I know, been reported upon in chloroform cases.

The idea that metabolism is responsible for the effects of anaesthetics would support the explanation given above. Whether the administration of an anaesthetic will set up acid intoxication would appear to depend, not upon the nature of the disease, nor upon the nature of the operation, but upon the
condition of the metabolism of the patient. That acidosis is dependent upon metabolism is shown by a consideration of the 612 cases which were examined. In 616/70 it found acetonuria—in 616/70 it was not until 12 hours after admission.

The large majority of these cases were given a different diet in hospital from that which they had had before admission. In most of the cases, the change was from breast feeding to bottle feeding. The condition of acetonuria lasted, as a rule, about 3 days.

31 They came to the conclusion and, I think, with reason, that the acetonuria was due to the inability of the child to metabolise its normal diet properly. When it had become used to the diet, the acetonuria passed off, on an average, in 3 days' time.

With a view to correlating the condition
of the urine before and after the administration of an anaesthetic; the clinical condition of the patient before and after operation, and the anaesthetic used. I have at the Manchester Children's Hospital Pendlebury carried out a series of observations, extending over a period of some nine months; and including 272 cases, to each of which a general anaesthetic was administered for the purpose of her forming an operation.

Of these 272 admissions
237 were non-septic cases
24 were tuberculous
11 were septic cases.

In 13 cases, that is 4.7% of admissions under observation; diacetic acid and acetone were found in the urine before operation.

Of these 13 cases.
11 were non-septic = 4.16% of non-septic admissions.
2 were tuberculous = 8.3% of tuberculous admissions.
0 were septic.
Acetic Acid and Acetone were found in the urine after ketosis in 143 cases or 52.5% of admissions under observation.

Of these,

121 were non-septic = 51.05% of non-septic admissions
14 tuberculous = 5.83% of tuberculous
8 septic = 72.7% of septic

All of the 13 cases with aseptic on admission were investigated as to circumstances at home. In 4 cases - weekly income of parents was 25-30/- in 9 cases - below 20/-

The average number of children per home was 3 and 3.5 respectively.

But of the cases with no aseptic on admission a much larger number was investigated and it was found that there were quite as many cases where the average weekly wage was below 20/- as there were with a wage above 20/-.

The appearance of the child on admission is of no significance as far as aseptic on admission goes.
The appended tables show the results of the observations upon the clinical condition of the child, and upon the urine, before and after operation, with particulars of the operation, and the anaesthetic.

The anaesthetics used have been chloroform, ether, and a 68 mixture; alone, or in some sequence, or following upon ethyl chloride.

The usual method of anaesthetising, and one eminently suitable for children, has been to give 3–5 c.c. or even 7 c.c. according to age, of ethyl chloride, by what may be described as the "ether" method. The ethyl chloride is squirted on to a piece of gauze folded in four layers. This is applied to the mouth and nose of the child.

As soon as the child is under, ether is poured on to the upper layer of the gauze, which is then turned over together. The ether is given drop by drop.
allowing it to percolate through the gauze. In some cases chloroform has been used to induce anaesthesia, and followed by A.B.E. mixture, or by ether.

In every case the anaesthetic is recorded, and the length of time the child was under the influence of the anaesthetic. The quantity of the latter is not recorded, as by the open method, it is impossible to gauge the amount lost by evaporation.

In the tables the following data are recorded:

Name, Age & Sex, Diet before operation.

Pulse, respiration and temperature, and condition of child before operation.

An analysis of the urine as regards the presence or absence of Albumin, Sugar, Acetone and Diacetic Acid before and after operation. Anaesthetic used, operation performed, length of time under the anaesthetic. A.B.E. or B.R. after operation, absence or presence of vomiting and its nature. General condition and remarks.

From these data it may be possible to form an idea as to the effects of anaesthetic, diet, and
operation upon the patient.

From these tables one is led to form the following opinions

1. That the presence of diabetes, per se, has little to do with the presence of acetoneuria, since none of the 11 septic admissions had acetoneuria. But a septic case is more liable to suffer from acetoneuria than a clean case after operation. That a tuberculous case is about as liable to so suffer as a clean case. Thus 72.7% of septic admissions had acetoneuria after operation, whereas in tuberculous, and clean cases, the percentages were 35.3% and 32.5% respectively.

2. Of cases with no acetoneuria after operation, 41 had only 8C + E; whilst 6 had chloroform at one part of the operation, i.e., 35.3% of cases with no acetoneuria had 8C + E.
Of the cases with diaceturia after operation, but not before (it would not be right to compare those that had diaceturia before operation); 43 had had Ethyl Chloride and Ether; and 87 had had chloroform at some stage of the operation.

i.e. 38.3% of cases without diaceturia had had EC + E + 62.6% ......... chloroform

while 33.07% of cases with diaceturia had had EC + E + 66.9% ......... chloroform

These figures point to the nature of the anaesthetic used, whether chloroform or Ether, as being of little importance, so far as the production of Diaceturia is concerned.

3 of 30 cases that developed symptoms; 23 had had chloroform during some part of the operation; and 7 had had only EC + E, pointing to the fact that the use of chloroform is not more apt to produce Acidosis, but is apt to produce Acid Intoxication more than is the use of Ether and Ethyl Chloride.

The recognition of this condition is of importance. As is at present understood by "post-anæsthetic poisoning," one means those fatal cases which have been reported at various times.
Barbar and Lagenbeck in 1850, gave it as their opinion that some deaths occurring after the administration of chloroform were due to the delayed poisonous effects of the latter; cases having occurred in Barbar's practice which were unexplained to recover rapidly; and the issue of which could not be otherwise explained.

Little more was heard of the subject until 1854, when Ferrier explained the frequent presence of albumin in the urine after the administration of chloroform, as caused by some toxic agent.

Before this, in 1852, Lee had published a series of cases as being those of recurrent vomiting or pyloric vomiting.

Much attention has since been paid to these cases of acute intoxication, especially to those of pyloric vomiting.

In America, Snow in 1893 gave an account of cases of frequent vomiting in children and in 1903 Peason discussed the relation between such vomiting, and the presence of acetone and diacetic acid in the urine.
considers the condition produced by acetone in the blood; and Gustave Smith in 1906 discusses, in the same journal, the same subject.

On the Continent, cyclical vomiting has been worked at by Richardière and Gilbert; whilst the after effects of anaesthetics have been discussed by Eisenmuth, Bastianelli, Kranzberg, and others.

Cyclical Vomiting

is a condition met with occasionally in children, and a description of a typical case is given in Nolde's Encyclopaedia of Practical Medicine.

From a condition of apparent health, the child becomes suddenly languid, and has a moderate elevation of temperature accompanied by vomiting that is persistent, and sometimes violent.

There soon develops prostration, and a fatal issue of the case seems not improbable, cats suddenly as it began, the vomiting ceases, and the child is rapidly restored to health. Occasionally a definite cycle is set up.
After the stomach is free from food, the vomited substance appears to be pure gastric juice; and in several cases there is a high degree of acidity. Solens of Paris expressed the view that the affection depends upon some disturbance in metabolism — with excessive development of uric acid.

Nolangel thought that the disturbance in metabolism is an accompaniment, and not a cause, of the vomiting.

Diacetetic acid is found in the urine.

He recommends treatment by saline, lavage of the stomach, and the administration of sedatives.

Conditions of Fatty acid intoxication.

There are many symptoms which are common to instances of acute poisoning, the coma of diabetes, poisoning by phosphorus, cyclical vomiting, and acute yellow atrophy of the liver.

From the fact that so many conditions have symptoms which are similar, it would seem that there must be a cause which is common to them all. Diacetics is common to
them all; and this points to the common cause being one of altered metabolism.

That a disturbance in metabolism is the cause of diaceturia is shown by Brem's Investigations; in which he proves conclusively that by changing the diet of infants, diaceturia can be produced— which passes away as the infant gets used to the change of food. This leads one to inquire whether there is any relation between diaceturia after the administration of anaesthetics, and the number of days which the child has spent in hospital previous to operation. From the cases under my observation it is seen that in the 130 cases that had diaceturia after operation, but not before— the number of days in hospital previous to operation being divided into groups as below —the number of cases in each group was:

<table>
<thead>
<tr>
<th>Days in Hospital previous to operation</th>
<th>Num. of cases with diaceturia after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>same day</td>
<td>4</td>
</tr>
<tr>
<td>1 day</td>
<td>17</td>
</tr>
<tr>
<td>2 days</td>
<td>49</td>
</tr>
<tr>
<td>3 days</td>
<td>44</td>
</tr>
<tr>
<td>4 days</td>
<td>6</td>
</tr>
<tr>
<td>5 days</td>
<td>1</td>
</tr>
</tbody>
</table>
Of those with no diacetic acid neither before nor after operation.

Days in bed previous to operation | Number of cases
--- | ---
Same day | 3
1 day | 9
2 days | 39
3... | 47
4... | 6
5... | 5
6... and upwards | 20

There is little difference between the two tables except in the last group of six days and upwards.

But, taking the 30 cases which showed first symptoms with the presence of diacetic acid, we have

Days in bed previous to death | Number of cases with acetic intoxication
--- | ---
Same day | —
1 day | 8
2 days | 16
3... | 6
4... | —
5... | —
6... and upwards | —

This shows that the length of stay in hospital previous to operation is of importance, not in relation to the presence of diacetic acid in the urine, so much as in relation to the presence of symptoms of acetic intoxication.
The stay in hospital prior to operation is probably of 
inimportance on account of the dieting; and still more, 
on account of the condition of the bowels. 
Many of the cases admitted into hospital are 
habitually constipated to a greater or less degree; 
If this be not corrected before operation we get 
acidification more easily set up when an 
anæsthetic is administered. 
It is not enough to give the usual purge, and enema 
just before the operation." The stools of the 
intestines must be corrected; and for this to be done 
it is necessary that the case should be in 
hospital at least 3 days before operation. 
This is of importance in view of the readiness of 
some surgeons to operate on many cases in 
the out-patient department of a hospital. 
(See letter in the B.M.J. March 10th, 1913. p. 471.)
For little regard is paid to the after effects of the 
anæsthetics; and it ought to be more generally 
recognized that by operating at out-patient 
departments on cases that require general 
anæsthetics, there is not only a risk of 
syphilis, pneumonia setting in from exposure to cold 
and wet, but also a risk of post-anæsthetic 
poisoning.
That this risk is not an imaginary one has been proved, at all events, to my satisfaction, at this hospital, where, out of 272 cases that had an anaesthetic, at least 38 or 11½ gave cause for anxiety from the after effects of the anaesthetic.

Classification of post anaesthetic poisoning.

Post anaesthetic poisoning may be classified as follows according to the severity of the symptoms:
1. Slight cases, with diuresis, sometimes a little vomiting, but no collapse.
2. More severe cases, with diuresis and tachycardia.
3. Severe cases, as unusually described in text books, and are usually fatal.

Up to the present time class 3 has been most generally recognised.

In 1904, Stiles drew attention to cases where children had died without apparent cause, within 2 or 3 days after an operation. Since then more attention has been paid by surgeons to this serious condition.

Post chloroform poisoning is the term usually applied.
to this condition.

The operation for which the anaesthetic is given may be only a slight one, and of slight duration. About 24 to 36 hours after the operation, the child vomits some dark coffee ground-like substance, and becomes restless. The temperature is usually raised a little, and the pulse becomes frequent. There may be jaundice, and the breathing may become hurried, usually at a later stage. There is often a smell of acetone in the breath, and the urine, as a rule, contains diacetoic acid, but not always. The child becomes restless, and faintly delirious, vomiting continually. He becomes weaker, and more and more collapsed until he loses consciousness, breathing is now stertorous, and death in this comatose condition.

The post-mortem appearances usual systemic fatty degeneration of the liver, and sometimes of the kidneys, and the heart muscle. The symptoms are by no means stereotyped, and that looks often convey a wrong impression of the clinical picture of chloroform poisoning from the dogmatic manner in which they
enumerate the symptoms. Thus the length of time after the operation before the symptoms develop may vary as much as 5 - 40 hours. 

Not long after the animal, fatty degeneration five hours after the administration of chloroform. In a case which occurred at this hospital in 1912, the first symptoms came on eight hours after operation. Then the presence, in the urine, of acetone and direct acid is not invariable, as in the case recorded below. This may explain the severity of the symptoms in such cases. Where the acids are excreted well, less demand is made upon the functions of the body, and so metabolism is not so much interfered with. The breathing may not be hurried; indeed, some observers say that this is a peculiarity of the condition - that though the pulse is affected, the breathing is, except at the end, when coma sets in; unaffected and regular. Jaundice may be present, but is often absent. Again, the postmortem appearances are not constant. Fatty degeneration of the liver is usually seen,
and is usually the most marked; but Troeschel
records a case where the liver was not affected,
but where the heart and kidneys were
degenerated.

The brain was examined in a case by Aubertin,
and found to be normal.

Achry (1824) examined the brain in a case also
and found it was normal.

Case described.

A case of severe post-anaesthetic poisoning
occurred at this Hospital in August 1912.

Alice Lindley, aged 10 years, was admitted on
the 14th August 1912, suffering from

Spastic Diplegia.

She had had whooping cough in infancy,
but no other infectious disease.

Her previous history was one of cerebral ataxia
and a congenital paralysis. She did not
attempt to walk until she was two years old.

She had no incontinence.

Her general condition on admission was good.

There was nothing abnormal in the respiratory
and circulatory systems.

She was fairly intelligent, and her memory
was fair.
She had all the signs of a spastic diplegia.

On the 16th August, 1912, she was operated upon, after having been prepared by oil the night before and enemas on the morning of the operation.

There was no diacetic acid, nor acetone in the urine before operation.

She had boiled to drink at 5.30 a.m.

The operation commenced at 9.30 a.m.

Mr. Roberts exposed the roots of the lumbar nerves by removing the spines and laminae of the lumbar vertebrae, and incising the meninges.

The posterior roots of the 1st, 2nd, 4th and 5th lumbar nerves were gently raised over tubular dissector, and divided close to the cord, a good deal of cerebrospinal fluid escaped.

The meninges were sutured with interrupted silk sutures. The muscles were sutured with catgut, and the other wound closed with a continuous suture.

The patient took the anaesthesia well; during the latter half of the operation very little chloroform was needed. At one time she appeared to be in a condition of coma, but she recovered quickly.
The anesthetics were a 68 mixture and chloroform; and the time under their influence was sixty-five minutes.
The operation was performed on strictly aseptic lines, and no anti-aseptic was used throughout the operation.
The pulse was very feeble when the patient left the theatre.
She was immediately given a neutral saline, and recovered very quickly. The body became warm, and the pulse good.
She vomited a little bile fluid after coming around from the anesthesia, and again half an hour later.
At 4 o'clock, six hours after operation, she vomited some dark coffee-ground like fluid, and again at 4:30.
The pulse was frequent, 120 per minute, but of good quality.
At 5 p.m., there was a lot of roving through the dressing, and this was packed. The child was quite intelligent, and seemed to be fairly fit. She was drinking a lot, but kept little down.
At 5:30 p.m.—ten hours after operation,
The pulse was not so good, and more frequent, 130 to the minute. The child was restless and thirsty.

She was put on two hourly salines per rectum and retained the first.

At 10 p.m., she was not in good condition. She was restless, and complaining of thirst. The wound had been packed again.

She vomited dark fluid at intervals; Neptuine m & X was given by mouth, and subcutaneous saline into the axilla.

The pulse improved a little. Sodium bicarbonate gr XX was given by mouth at 1 a.m. midnight.

At 5 a.m., next morning, the pulse was very feeble. Adrenalin m X was injected hypodermically, and also brandy m X.

The patient was delirious and excitable, the breathing stertorous, and hurried.

 Intravenous injection of saline was arranged for; but the child died before it could be given.

A post-mortem examination was made.

The Thymus gland was large, weighing just under one ounce.
The heart muscle was pale and flabby. There was some thickening of the endocardium over the aortic valves.

The lungs showed nothing abnormal. The liver showed marked fatty degeneration, and the kidneys also showed fatty degeneration.

The stomach contained dark fluid. The wound was healthy, a little serum and areolar and visceral fluid was on the dressing.

There was no diacetic acid, nor acetone in the urine.

The above, in many of its symptoms, and in the appearances found post-mortem, is typical of group III, severe cases of post-anæsthetic poisoning.

In this case I wish to draw more attention to the less severe cases of poisoning after the administration of anaesthetics, the cases of group II.

Symptoms often develop in children who have had anaesthetics. It may be ether alone, or chloroform alone, or various combinations of these.

These symptoms may go on to a fatal ending, and, no doubt, have done so; but the unhappy issue has been attributed to delage de shock, or some such mysterious condition. They have not been recognised as cases of post-anæsthetic poisoning.
Even if the symptoms do not end fatally, they give rise to anxiety on the part of the person who is in immediate charge of the case; and who, from want of knowledge as to the case; and, therefore, as to the proper treatment of these symptoms, is caused considerable alarm.

These symptoms may be described as they occurred in the case of a girl named Donald, aged 6 years, who was admitted to hospital three days before the operation. The complaint was genu valgum.

On admission her temperature, pulse, and respiration were normal, and her general condition was good.

She had the ordinary diet for children of this age up to the evening before the operation.

That evening she was given the usual aperient of Castor Oil; and a soap and water enema the following morning. She had no solid food three hours before the operation.

The anaesthetic used was ethyl chloride, followed by A.C.E. mixture and then ether by the open method. Gastrotomy was performed on the right thigh, and the time the patient was under the anaesthetic was fifteen minutes.

There was no sign of shock. The child recovered quickly from the anaesthetic, and was well for the rest of the day. The urine had been tested before operation, and contained no albumin, sugar, acetone nor diacetic acid.
The urine of the next morning contained acetone and diacetic acid. The quantity was not diminished. There was no vomiting.

Later in the day, thirty hours after operation, the child was noticed to be very quiet—the eyes were sunken, and the child had the facial appearance that one associates with acute abdominal cases.

The breathing was not altered, but the pulse was frequent; and the body felt cold.

The treatment adopted was: injection of normal saline per rectum, three oranges every two hours for twenty-four hours, then four hourly for 24 hours. Large doses of Sodium Bicarbonate were given per rectum, and also by the mouth in doses of gr. \( \frac{X}{X} \) 4 half.

The child recovered slowly; and in forty-eight hours was quite fit again.

The case described is typical of several that have suffered from the after effects of anaesthetics.

In recognizing the condition, the important points are the sunken eyes, and the frequency of the pulse.
One can say, almost with certainty, that, if a child has had an anaesthetic, and, a day or two, develops this facial appearance of the sunken eyes; that child has diuretically and acetone in the urine; and is suffering from the toxæmia of acidosis—which must be energetically treated.

The accompanying temperature chart No. A shows the relation of the temperature, pulse and respiration in the case described.

It is seen from this chart, that, whilst the temperature rose but little after the operation, the pulse became more rapid in frequency and remained frequent for forty-eight hours.

The respiration rate was not altered.

Chart B demonstrates the frequency of the pulse in a similar case.

As a rule, the temperature, in these cases, is not affected to any degree corresponding to the gravity of the symptoms.

But in some of the cases, which were under
my observation, the temperature was affected to a marked degree.

A boy named Williams, aged 5 years, was admitted on the 25th of September 1912, suffering from Tonsils and Adenoids. After the usual preparation, he was operated upon the following day. The anaesthetic used was Ether by the open method; and the length of time the patient was under the anaesthetic was seven minutes. The boy took the anaesthetic well; and was none the worse immediately after the operation, which consisted of the removal of the tonsils and adenoids by the guillotine and curette.

There was no laetic acid in the urine previous to operation.

That night the boy was restless; his temperature rose to 102°F. and the pulse was 136 per minute, the respirations being 25 per minute.

In the morning following—27th—the child...
looked very ill.
The eyes were sunken; and the child was collapsed. He would take nothing except water, and milk; which he drank, in small quantities, at frequent intervals.
There was nothing in the throat to account for the condition.
The urine contained diacetic acid, and acetone in large quantity.
The temperature came down during the day to 99°. The pulse remained frequent, 120 per minute.
The night of the 27th, the temperature again rose to 103.2°; and the pulse was 140 per minute; the respirations being not more than 28 per minute.
The child had been restless during the day, but later became quiet, lying on his back, taking no notice of what went on around him. The breathing was regular and quiet. The pupils were very small. They were equal, regular, and both reacted to light.
There was no vomiting.
The child was able to swallow when fed.
The treatment adopted was the injection of normal saline per rectum, and the syrup of glucose was given, both in the saline, and by the mouth. This treatment was started in the morning of the 27th.

On the evening of the same day, Sodium Bicarbonate was given as well, gr. XI being given every two hours by the mouth.

It was not until the Sodium bicarbonate was added to the other treatments, that any improvement in the condition of the patient took place.

In 48 hours the boy had recovered and was himself again.

Chart C is a copy of the chart in the case just described.

Chart D is that of a case which had diacetic acid in the urine prior to operation.

Ag. Wm. Sewell. Burns, aged 7 years, was operated upon for tubercular abscess of the hip joint.
She was operated upon the day following admission.
The abscess was incised and scraped. The time under the anaesthetic was fifteen minutes.
The anaesthetics used were Ethyl Chloride followed by Ether, and then Chloroform.
The patient appeared to be none the worse after the operation.
Two hours after the operation the child vomited some brown fluid; and again an hour later.
At 12 midnight, she had all the appearance of acidosis poisoning. The eyes were sunken, she lay on her back, not sleeping, but taking no interest in things around her.
The pulse had become frequent, and she vomited frequently, chiefly dark red fluid.
She was immediately treated with rectal Salines every 2 hours, containing Sodium Bicarbonate.
Nothing was given by the mouth; and lavage of the stomach was ordered to
to be carried out if the frequent vomiting continued.

Diuretic acid was present in the urine in large quantity.
The next day syrup of glucose was given in the salines which were injected every 4 hours.

Twenty four hours later the vomiting had ceased, and the salines were stopped.

Sodium Bicarbonate and glucose were given by the mouth for another 24 hours when the child had completely recovered.

Chart 8 shows the same frequency of the pulse in a case similar to those already described.
Treatment of Post-anaesthetic Poisoning

The treatment of all cases of post-anaesthetic acetonyxia is the same.

In every case it is
1. to prevent the evil effects of the formation of diacetic acid.
2. to prevent the formation of diacetic acid.

As already pointed out, the acetone bodies are not in themselves dangerous. The danger lies in the fact that the acetone bodies, if not excreted by the kidneys in sufficient quantity, or if not neutralised by the alkalies of the diet; use up the nutritions of the body and thus lead to protein disintegration — producing the poisonous bodies which act upon the liver. As a consequence, the liver cannot utilise the carbohydrates, and therefore the fats are not properly oxidised, forming various circles.

It must then be our object in a case of
acidosis to first of all neutralize the pyruvic and diacetic acids, and so prevent them from drawing upon the tissues of the body. This is done by giving normal saline and sodium bicarbonate.

In this way the liver is relieved, and in a short time regains its power of utilizing the carbohydrates. It is thus obvious that it is of little use to start the treatment of these cases by giving glucose; since the liver is not able to use it until it has been released from the poisonous effects of the bodies produced from the disintegration of the protein molecule.

When normal saline solution and sodium bicarbonate have been given for 24 hours - then the second part of the treatment may be carried out - the prevention of the formation of more diacetic acid.
This is done by supplying oxygen for the complete metabolism of the fats.
This is done by giving glucose—a form of carbohydrate which is easily used up by the liver.
In this way the fat is supplied with oxygen and is changed into the ultimate products of water and carbon dioxide—instead of being incompletely oxidized, and forming body butyric and diacetic acids.

It may be well here to repeat the classification of cases of post anaesthetic poisoning (v. p. 37):
1. Slight cases, with Diaceturia.
2. More severe cases, with Diaceturia and toxicemia.
3. Severe cases, usually fatal.

The treatment of all these cases is essentially the same—but differs in each group in the promptness and thoroughness with which it must be carried out.
Group 1. These cases do not appear to be any the worse for the presence of diacetic acid in the body.

It is advisable, however, to give sodium bicarbonate and, later, in 24 or 48 hours, glucose, to all cases with diarrhoea. Sodium bicarbonate gr x every 4 hours for 48 hrs - followed by the syrup of glucose two to four drachms in water every four hours or three times daily is suitable treatment for a child of ten years.

Group 2. The treatment of these cases must be prompt.

It is advisable to give in the first place, bicarbonate gr III followed in four or six hours by magnesium sulphate gr x x in water flavoured with a little syrup of orange.

If there be vomiting it is better to give high enemas of soup and water.

The bowel must be emptied as much as possible.

After the enemas have acted normal saline solution containing...
Sodium bicarbonate, a draught of the powder to the ounce of saline, should be injected per rectum. Four fluid ounces of this solution should be given at least every four hours to a child of ten years.

If there be much collapse, three fluid ounces may be given every two hours. These saline should be given every two or four hours for 24 hours.

Thin glucose should be given in large doses. Half an ounce of the syrup of glucose may be given in water by the mouth, or an ounce per rectum every four hours. This should be continued for 2 or 3 days after the collapse has passed off.

In cases where collapse is very marked I have given adrenalin - in 1/1000 solution hydromically - with good result.

And when there is sign of heart failure the inhalation of oxygen passed through a jar containing absolute alcohol, and standing in warm water - has done good.
Group 3.

The treatment here must be still more energetic.

These cases are recognised from the incessant vomiting that starts shortly after the operation, the heatlessness, the delirium, and the proximal coma. It may be unnecessary to draw a distinction between cases of group 2 and those of group 3—beyond saying that the symptoms of the last group are more urgent and severe.

The treatment must, likewise, be more urgent.

Two hourly salines as described for group 2 should be given; and if not retained, subcutaneous salines should be given, or even intravenous injection of saline solution. Lavage of the stomach should be carried out, and some saline solution may with advantage be left in the stomach.

Stimulants should be given with caution. Strophanthoside B.P. m. 2. every 3 hours, is best.
for a child of 5-10 years, given under
the skin.

Strophanthin gr. 200, hypodermically
every four hours, is also good.
As regards the presence of albumin in the urine after the administration of anesthetics, Hegar and Malten-Burch are said to have found albumin present in the urine after giving chloroform in 30% of their cases, and Friedlander is said to have found albumin in 42 out of 56 cases.

Table IV shows the figures obtained on this point.

In one case there was albumin in the urine prior to operation. I will, therefore, neglect that case.

In 23 cases out of a total of 172, or 8.47%, albumin was present after operation, a positive result being obtained on heating the specimen and adding Acetic Acid.

In 10 of these 23 cases the anesthetics used were Ethyl Chloride and Ether, but no chloroform.

In 13 cases some chloroform was used.

The greatest length of time the child was under the anesthetic was 35 minutes. In none of these cases did the albuminuria persist more than four days; and in none...
was any bad effect noticed on account of it.  

acute nephritis occurred in none, and although acute nephritis is said to be set up by the administration of Ether, it has not occurred in any of these cases under observation.

I attach little importance to the above figures in regard to albuminuria, as the length of time under the anaesthetic was in no case great.

Administration of Anaesthetics, and the presence in the urine, of sugar.

I have not once found sugar present in the urine in children, neither before, nor after operation.
Summary of the observations made, and the conclusions one may draw from them.

1. It is important that a patient who is to have an operation, should be kept under observation for at least three days.

2. The urine of the patient should be tested before the operation, every day, for Albumin, Sugar, and Diacetic Acid. This is now the routine practice at the Manchester Children’s Hospital — the urine of all patients being tested for Diacetic Acid, etc., previous to operation.

3. If Diacetic Acid be present — the patient should be given Sodium Bicarbonate, and glucose a day later.

   or, if the operation is not postponed, chloroform should not be used as an anaesthetic, nor a b. s. in misuse, if it can be avoided — as

4. It is found that chloroform causes
diuretics in a slightly greater number of cases than do Ethyl Chloride and Ether, but it causes severe symptoms in a far larger number than the latter anaesthetics.

5. It is important that the bowels of the patient should be got into good order before operating — and therefore as few operations, requiring a general anaesthetic, should be done at outpatient departments as is possible.

6. The urine should be tested regularly after operation for diuretic acid.

7. Close watch should be paid by the ward staff, to the facial appearance of all cases after operation.

8. The frequency of the pulse must be carefully recorded before and after operation.
If acidosis, or acidosis with toxemia, should set in, the treatment described above must be carried out. Only by recognizing the condition and by treating it quickly can we save those cases which will otherwise be put down to some mysterious internal condition.
References to Authors quoted. I

2. Ibid. p. 173.
5. Ibid. p. 295.
8. Ibid p. 120.
9. Ibid. p. 121.
13. Ibid p. 121.
15. Ibid p. 121.
16. Ibid p. 120. Arch. f. physiol. u. pathol. 1915.
   Milroy on Digestion. Vol. 2. p. 327.
References to Authors quoted. II

   "Les accidents tardifs du chloroform. (Thooft)" p. 53.
33. Ibid p. 2.
   By Leonard Guthrie. p. 1168-1169.
List of Tables

Tables I and II

give particulars of cases that had no diaceturia:
either before, or after operation.

Tables III and IV

give particulars of cases that had
no diaceturia before operation;
but had diacetic acid in the urine
after operation.

Table V

gives particulars of cases that had
diaceturia both before and after operation.

Table VI

gives particulars of cases that had
albumin in the urine after operation.
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**Table II**

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<td>Zygomatic</td>
<td>Maxillary</td>
<td>Ethmoid</td>
<td>Sphenoid</td>
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**After Operation**

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</tbody>
</table>

**Note:** The table above shows the number of operations performed on the various sinuses before and after the operation. The operations were performed on the frontal sinus, zygomatic, maxillary, ethmoid, and sphenoid sinuses.
<table>
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<tr>
<th>Name</th>
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<table>
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<tbody>
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Note: Table IV and Table IX contain data related to wine consumption before and after an operation. The columns represent different wine types and their respective amounts consumed. The total amounts are also recorded.
### Before Operation

<table>
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<th>Name</th>
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<th>Operation</th>
<th>Remarks</th>
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### After Operation

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### Table VII

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