A STUDY OF TWO TYPES OF VOMITING ASSOCIATED WITH ACETONURIA.

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In the present paper are recorded observations on two main types of vomiting occurring in children, which are accompanied by acetonuria. The first part of the paper deals with some theoretical considerations and the second part with a series of actual cases which have come under my notice. The study of these types of vomiting is of interest not only from a clinical point of view, but also from a biochemical standpoint, it being possible, as described later, to follow certain metabolic processes occurring during the attacks, by means of simple analyses of urine.

I. Theoretical Considerations.

It will not be out of place at the outset to refer to the difference between "acidosis" and "ketosis" and their relation to alkali reserve. Acidosis was at one time referred to as a condition in which acetone bodies are present in the urine, but this state is more correctly called ketosis. From a clinical standpoint acidosis may be looked upon as a condition in which there is an abnormal tendency for acid products of metabolism to accumulate in the blood and tissues.

The two conditions may occur side by side, but acidosis is frequently preceded by ketosis, and if in such cases the alkali reserve is maintained by suitable treatment, including the administration of bases, this tendency for acids to accumulate may be rapidly checked.

The importance of recognising conditions where acid formation is increased cannot be over-estimated, for comparatively small variations in the *p*H of blood are incompatible with life. This fact is well illustrated by the many observations recorded in Michælis[1] where the value of *p*H for blood in numerous diseases isgi ven. In only one case[2] does this depart to any great extent from the value in health, 7·3—7·5, namely, in a case of diabetic coma where just before death the values for two determinations were 7·11 and 7·13. De Wesselow[2] quotes a case where the value was 6·98 in a patient with diabetic coma who subsequently recovered under insulin treatment. The *p*H of urine on the other hand may vary within much wider limits, and without serious consequences, the kidneys helping to remove accumulating acids from the blood and tissues.

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Group 1. *Cyclic or Recurrent Vomiting.*

The main features of this disease have been so ably dealt with by numerous writers that it is unnecessary to refer to them in great detail, but a few references may be given.

J. P. C. Griffith[3] considers that the condition is a toxic neurosis occurring in especially predisposed children, and due to disordered metabolic processes with inability to assimilate fat.

Ewing[4] considered it to be due to a poisoning from the intestinal tract, with resulting imperfect oxidation of fats.

Richardiere[5] states that the occasional occurrence of icterus has led some to believe that the liver is at fault.

H. C. Cameron[6] in a recent paper, referring to the characteristics of the child subject to cyclical vomiting, writes: "such children often, if not invariably, have certain temperamental and certain physical peculiarities which render their immediate recognition not at all difficult."

H. Membrat[7] agrees with Marfan in considering the cyclic vomiting of the Americans and the vomiting with acetonæmia as forming a single morbid entity, and in the course of his paper refers to the influence of parentage on this disease, the parents having frequently sedentary occupations.

I am strongly inclined to the view that true cyclic vomiting is a clinical entity, associated with a nervous diathesis, and not merely a form of vomiting accompanied by acetonuria.

An outstanding symptom of this condition is the recurrence of attacks of severe vomiting at fairly regular intervals, the exciting cause being some alimentary disturbance, over-exertion, or mental strain. In a severe attack the patient becomes comatose, and in even the milder attacks some drowsiness is usually present. This is probably, at least in part, due to the presence of acetone in the blood, the chemical constitution of this body giving it hypnotic properties.

It has been suggested[8] that adsorption phenomena play an important part in the action of such substances as this, and also that alimentary toxins are adsorbed by the cerebral tissues. The general severity of the symptoms may also be due to some extent to absorption by the bowel of small quantities of undigested protein which act as allergic substances and produce shock. In support of this view is the fact that joint pains occur as in serum disease.

An important question arises as to how many attacks of sickness should warrant the diagnosis of cyclic vomiting. I have personally seen few children who have had a sufficient number of attacks to justify such a diagnosis, but have seen a considerable number of cases which I have placed in the next group.

Group 2. *Severe Acetonuric Vomiting due to Digestive Disturbances.*

Under this heading I refer to an acute alimentary disturbance associated with acetonuria, but in which no neurotic basis is evident.

Some authorities do not definitely distinguish between this condition and true recurrent vomiting, but John Thomson[9] draws attention to "physiological acetonæmia" which has some points in common with the type of disease here described. When we consider that during early life the digestive mechanisms have not reached their maximum degree of efficiency, it is not surprising that at this time disorders of metabolism are quite common.

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In the practice of pædiatrics one of the most difficult problems which arise is that of advising suitable food for infants and young children, and the failure of mothers to grasp the principle of physiologically balanced feeding is frequently the underlying cause of digestive disturbances during childhood.

The main symptoms exhibited by children suffering from this type of vomiting are very similar to those described under cyclic vomiting. There is a considerable variation in the degree of severity of an attack, and in some cases the acuteness of the symptoms causes great alarm to parents.

The most important point in differential diagnosis is that the number of attacks is usually limited to one or two, which does not justify the term "cyclic" or "recurrent."

I consider that cases belonging to this class are not uncommon and are possibly diagnosed as cyclic vomiting or acidosis. They are often referred to as bilious attacks by the parents.

II. Clinical and Chemical Investigation of Cases.

A very large number of researches has been carried out on the value of blood analysis in diseases of metabolism, and many valuable results have been obtained; in pædiatric practice, however, the main objects of the clinician should be to hasten the recovery of sick children and prevent future recurrences of disease, and it is not justifiable to take frequent specimens of blood as a routine practice when the course of a disease can be followed by simple methods.

In the investigations here described a method of urine analysis has been adopted which was referred to in a short paper[10] read before the Children's Section of the Royal Society of Medicine in 1923 and has been discussed in greater detail [11,12] in two subsequent papers.

The ratio Ra referred to actually denotes the relationship between free and ammonia-combined acid in the urine, and is obtained as follows:—

25 c.cm. of urine are titrated with decinormal sodium hydroxide solution, using as indicator phenolphthalein; this gives the free acid value. Then to the same solution neutral formaldehyde solution is added (Folin's method) to liberate ammonia-combined acid which is then titrated with the same alkaline solution.

Ra is obtained by dividing the second titration by the first. The ratio is not reliable when determined during the administration of alkalis.

Acetone is tested for by adding to the urine a few drops of freshly-prepared solution of sodium nitro-prusside, acidifying with glacial acetic acid, and floating ·880 ammonia solution on the top of the mixture. A magenta ring forms at junction of the two liquids in presence of acetone.

The above titrations to obtain the ratio Ra are extremely simple, and can be carried out rapidly after little practice. They enable the physician to correlate the clinical and the bio-chemical events during the course of an attack.

It will be commonly found that during early stages of the "attacks" described later, acetone may be detected in the urine before the magnitude of Ra is increased, pointing to the probability of a good alkali reserve (see Case 1).

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Case Records.

Group 1. *Cyclic Vomiting.*

Case 1. I have been able to obtain early morning specimens of urine from a little girl who undoubtedly suffered for several years from true cyclic or recurrent vomiting.

These attacks were originally considered to be " bilious attacks " until more careful consideration was given to the case and numerous analyses of her urine were made. The patient possesses a very nervous disposition, and worries over small matters; the attacks were associated with faults in diet, and physical or mental strain, one such attack being initiated by a prolonged railway journey. During each attack the patient was repeatedly and violently sick, the temperature being raised and pulse accelerated. These symptoms were associated with great prostration and various degrees of lethargy approaching coma; there were severe pains in the muscles and joints, and occasionally abdominal discomfort. One attack at the age of 8 years lasted 6 days, and a similar one at 11 years lasted for the same time. It is worthy of note than the child recently had a severe attack of a similar nature although now 13 years of age.

TABLE I.

Case I. Urine Analysis: Early morning specimens.

	Titration I.	Titration II.	Ra	Acetone Bodies.
In normal health.	7·3	7·9	1·08	Absent.
	16·0	16·0	1·00	,,
	15·1	16·0	1·05	,,
	14·0	15·0	1·07	,,
	11·5	14·2	1·23	,,
	14·8	16·8	1·13	,,
	16·7	14·6	0·87	,,
	9·0	10·0	1·11	,,
During attack.	9·5	11·9	1·25	Present
	14·9	31·6	2·12	,,
	13·0	23·2	1·78	Absent.
	12·0	16·5	1·37	,,
	8·7	13·0	1·49	,,
During another attack.	9·9	34·0	3·43	Present.
	4·8	21·5	4·47	,,
	6·1	25·0	4·09	,,
	10·2	16·0	1·56	Absent.
	12·2	16·5	1·35	,,
	11·2	15·1	1·34	,,

Case 2. This was a little girl, an only child, aged $5\frac{3}{4}$ years. There was a history of constipation, associated with occasional severe attacks of vomiting; a recent one being accompanied by albuminuria. When first seen by me she was very drowsy. T. 101°, and had vomited at half-hourly intervals. The bowels were constipated, and the urine contained albumin (·07 Esbach) and acetone bodies.

TABLE II.

Case 2. Urine Analysis: Morning specimen.

Titration I.	Titration II.	Ra	Acetone Bodies.
11·5	47·0	4·13	Present.

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The patient was discharged fit after six days treatment with alkalis and laxatives. I have been informed by the child's doctor that she has had a number of similar attacks since, and at the time of writing she is under my care in hospital for the same trouble.

CASE 3. The history of another case of true cyclic vomiting seems worth recording as the attacks have extended over a period of ten years.

The patient, a girl, aged 13 years, was seen by me recently after an operation for tendon transplantation; she had been vomiting frequently for four days after the operation and the urine contained large amounts of acetone bodies. Sodium bicarbonate and calomel soon relieved the symptoms, but as the administration of alkalis renders the value of RA unsatisfactory this ratio was not followed.

From the hospital records I found that she had a severe attack of a similar nature when 7 years old after tonsillectomy and the following year an attack simulating acute intestinal obstruction. Her mother also described numerous other attacks of acute vomiting.

Group II. Severe Acetonuric Vomiting or Toxæmic Vomiting of Childhood with Acetonuria.

As previously pointed out cases included in this group are relatively common. I have been able to follow a number of them, especially with reference to the variations which occur in the urine normally and during an attack. I propose to refer to several of these cases in some detail.

CASE 4. This patient is the younger sister of Case 1, but does not possess the same type of nervous temperament, and appears to be quite a normal child. She had a brief attack of acetonuric vomiting at 2 years of age and a much more severe one at 5 years. The latter attack started on the day following faulty feeding.

She was greatly distressed, very sleepy, pulse 140, respirations 36, temperature 102°, and complained of pains in the neck and joints. The urine on the first day of attack contained much acetone. The symptoms rapidly disappeared after administration of laxatives.

TABLE III.

CASE 4. URINE ANALYSIS: Early morning specimens.

	Titration I.	Titration II.	RA	Acetone Bodies.
In normal health.	3·8	4·7	1·23	Absent.
	23·0	20·0	0·87	,,
	16·1	16·3	1·01	,,
	4·4	5·4	1·20	,,
	5·0	6·0	1·20	,,
	22·7	21·8	0·96	,,
During attack and recovery.	31·30	37·5	1·19	Present.
	14·50	30·5	2·10	Absent.
	14·0	24·5	1·75	,,
	2·7	5·1	1·88	,,
	4·0	8·0	2·0	,,
	11·5	14·1	1·21	,,

The alkali reserve was doubtless diminished during the attack, but rapidly recovered on normal diet without administration of bases. The child has had no further similar attacks, and is now seven years old.

CASE 5. A girl aged 9¾ years. This case is of special interest since, although the symptoms on admission were identical with those observed in a severe case of cyclic vomiting, there was no history of recurrent attacks.

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When admitted to hospital the child looked extremely ill and collapsed. The respirations were those of "air hunger," the eyes were half closed, and the patient in a comatose condition.

When roused and questioned she complained of pains in the belly and joints. The tongue, tonsils, and uvula were covered with a dark brown deposit, the temperature raised and pulse accelerated.

The child was given a soap enema and then sodium bicarbonate, gr. 20, every four hours, and was very much better next day. A specimen of urine passed on admission was loaded with acetone, but as is frequently the case at the onset of such attacks gave no indication of acidosis (RA=0·91). Owing, however, to the serious condition of the child it was deemed wise to administer alkalis immediately, which prevented RA from being satisfactorily followed, as the urine soon became alkaline to phenolphthalein. The urine also contained a trace of albumin on admission, but this rapidly disappeared, as did the acetone bodies. She has had no further attack.

CASE 6. Patient, a boy aged four years, who had vomited a number of times before admission; on the day he entered hospital his urine contained acetone bodies. He was given no drugs but kept on low diet, and was discharged fit after seven days.

TABLE IV.

CASE 6. URINE ANALYSIS: Early morning specimens.

	Titration I.	Titration II.	RA	Acetone Bodies.
During attack and recovery.	6·3	15·7	2·47	Present.
	10·0	42·5	4·25	,,
	7·0	18·0	2·57	Absent.
	10·0	15·5	1·55	,,

His mother informed me eight months later that he was quite well, and that he had suffered from no similar illness either before or after the one described here.

CASE 7. This case is very similar to the previous one. The patient, a boy aged 5½ years, had vomited five times in the twelve hours before admission, and was constipated.

On admission his temperature was 101°, and his pulse rate 142. No further vomiting occurred; calomel was administered and early morning urine examined for three days. The results distinctly indicating acidosis the boy was given sodium bicarbonate for six days, and was discharged quite fit two days later. There was no history of any similar attack.

TABLE V.

CASE 7. URINE ANALYSIS: Early morning specimens.

	Titration I.	Titration II.	RA	Acetone Bodies.
First three mornings in hospital.	13·0	31·0	2·38	Present.
	11·0	39·0	3·54	,,
	4·0	28·0	7·0	,,
Morning of discharge	15·5	20·0	1·29	Absent.

CASE 8. The patient, a boy aged three years, had an attack of frequent vomiting, and on admission to hospital his urine contained acetone bodies, and his temperature was 101°.

He was placed on low diet and treated with calomel. As the ratio RA was not diminished by this treatment he was given sodium bicarbonate and rapidly improved.

I was unable to elicit any history of other attacks, and ten months later his father informed me that he was in good health.

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TABLE VI.

CASE 8. URINE ANALYSIS.

	Titration I.	Titration II.	RA	Acetone Bodies.
Before treatment with alkalis.	11·0	17·5	1·59	Present.
	11·5	22·5	1·95	,,
	6·5	15·5	2·38	,,

CASE 9. A girl, aged 8 years, had two attacks of severe vomiting within two months. On both occasions the sickness was associated with drowsiness, raised temperature, accelerated pulse and acetonuria.

On the first occasion she was treated with sodium bicarbonate and calomel, and on the second occasion with calomel and glucose without alkalis. The analyses of several early morning specimens of urine during attack and recovery serve to demonstrate that the ratio RA is not reliable during administration of alkalis.

TABLE VII.

CASE 9. URINE ANALYSIS: Early morning specimens.

	Titration I.	Titration II.	RA	Acetone Bodies.
Under alkaline treatment,	17·5	26·5	1·51	Present.
	9·0	24·5	2·72	,,
	2·5	6·5	2·60	Absent.
Under glucose treatment.	9·0	32·0	3·55	Present.
	12·0	26·0	2·17	,,
	16·5	31·0	1·87	Absent.
	11·6	17·0	1·46	,,

On both occasions recovery was rapid, and nine months later the child was in good health, and had not suffered from a similar illness in the interval.

CASE 10. A little girl aged 15 months, who had vomited eight times in twenty-four hours. On examination the child was very irritable, temperature 101°, pulse 160. She had been given an excess of milk and eggs for some time. An examination of the urine gave following results :—

TABLE VIII.

CASE 10. URINE ANALYSIS.

Titration I.	Titration II.	RA	Acetone Bodies.
13·5	49·0	3·62	Present.

Calomel and sodium bicarbonate were administered at once and the patient was virtually normal next day. The child had a similar but less severe attack nine months later, but her doctor informs me that since this she has had no more attacks, and she is now three and a half years of age.

CASE 11. In this case the patient was a little girl who suddenly became ill after over-indulgence in rich diet. She was violently sick, temperature raised and pulse rate much accelerated, and finally lapsed into a lethargic condition. The urine was mixed with vomit and could therefore not be examined quantitatively, but gave well marked reactions for acetone.

Administration of calomel restored her to an almost normal condition next day, despite the severity of the attack. She had no similar attack previously, and three years later her doctor informed me that she had experienced no further trouble of the kind.

It is well to remember that the early stages of tuberculous meningitis may simulate acetonuric vomiting. Such a case was referred to me, and a urine examination gave :

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TABLE IX.

TUBERCULOUS MENINGITIS. URINE ANALYSES.

Titration I.	Titration II.	RA	Acetone Bodies.
10·0	30·0	3·0	Present.

Shortly afterwards typical signs of tuberculous meningitis were present, and the patient died within a week.

It would be unprofitable to describe in detail further cases belonging to this group, but they frequently come under my observation, and I have a number of records of patients in which only one or two attacks were observed but which were very severe and caused much anxiety to the parents. The symptoms observed in such an attack are clinically indistinguishable from those noticed in one of the periodic attacks occurring in true cyclic vomiting.

It is worthy of note that there is nearly always a history of marked dietetic indiscretion preceding the attacks. The treatment is by means of low diet, aperients, and rest, with the addition of alkalis if indicated by severity of the case or by urine analysis.

SUMMARY.

Two types of acetonuric vomiting in children have been described, and special reference has been made to the urinary findings in each type.

It has also been shown that the course of the disease can be followed by means of simple urine analysis. In both types a variable degree of acidosis and ketosis is observed.

The ease with which these conditions develop in children is responsible for some of the symptoms described, and points to the necessity for early administration of bases in many cases.

I have ventured to draw a very definite line between true cyclic vomiting and severe acetonuric vomiting, as this distinction appears to be justified by careful investigation of the clinical histories.

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