KETONÆMIA, CYCLICAL VOMITING AND SOME NERVOUS DISTURBANCES IN CHILDREN.

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Ketonæmia and Hypoglycæmia.

In 1911 Frew⁽¹⁾ drew attention to the great frequency of ketonuria in the children recently admitted to the wards of The Hospital for Sick Children, Great Ormond Street. All clinical experience and all experimental work are in accord in recognizing that a significant ketonæmia occurs more readily in childhood than in adult life. The extensive literature concerning ketonæmia and ketonuria in children has been recently reviewed in the *Archives of Disease in Childhood* by Brown and Graham⁽²⁾ as an introduction to their own admirable work on the subject.

Acetone bodies commonly appear in the breath and in the urine of children (a) during infection marked by considerable pyrexia; (b) during fasting (c) during vomiting of such persistence and severity as to interfere with the intake of food; (d) after anæsthesia, and (e) upon a diet containing a great deal of fat and little carbohydrate.

Coincidentally with the rise in the amount of ketone bodies and with the corresponding fall in the alkaline reserves of the blood many observers have found a considerable fall in the percentage of blood sugar. Thus whereas in adults the blood sugar remains remarkably constant despite prolonged starvation, in children it would appear that there may be a considerable though sometimes shortlived fall and that in general the younger the child the more severe the fall. In a study of the metabolism of young children subjected to prolonged periods of fasting Shaw and Moriarty⁽³⁾ found that the ketosis, the fall in the plasma bicarbonate and the hypoglycæmia were all on a much greater scale than in adult life. There was indeed a definite fall in the pH value of the blood. In the later days of the fast some degree of compensation was achieved and the sugar content became less depressed. The depletion of the glycogen reserves would appear to occur more rapidly in fasting children than in fasting adults and the body appears unable for some time to bring about a glucose synthesis sufficient to maintain a normal blood sugar.

Upon children actually subject to cyclical vomiting as yet comparatively little work has been done. Hilliger⁽⁴⁾ in 1914 first detected a fall from 0.14 to 0.07 in the blood sugar in a child with cyclical vomiting accompanying the development of the ketosis. In a young child two and a half years old, the subject of typical attacks of cyclical vomiting, Ross, Hughes and Josephs⁽⁵⁾ found a fall in the blood sugar and of the CO₂ combining power of the blood, but noted that the recovery was so rapid that the hypoglycæmia could only be demonstrated during the height of the attack.

Wilson, Levine and Rivkin⁽⁶⁾ investigated the oxidation of the food stuff in a suitable group of six children one of whom suffered from cyclical vomiting. They found that children do not necessarily oxidise food stuffs in the proportion ingested, a circumstance which renders dietary data unreliable. Normal children usually oxidise a higher proportion of carbohydrate and a lower proportion of fat than they receive in their diet. The difference is most marked when the fat intake is relatively high. In the one child with cyclical vomiting this replacement of fat by carbohydrate derived from the stores of the body was much less obvious. The authors suggest that while normal children are by preference carbohydrate burners, readily replacing any excess of fat in the ingested mixture by carbohydrate, this power of adjustment is less developed in cases of cyclical vomiting. The subjects of this disorder are pronounced fat burners. If fat in excess of carbohydrate is provided, an attempt is made to oxidise all the fat and the necessary additional carbohydrate is not mobilised from the stores of the body. This peculiarity, it is suggested, may be the factor which explains the great ketonæmia in cyclical vomiting. Observations on this point are too few at present to permit any quantitative statement. The lower carbohydrate utilisation in the one child with cyclical vomiting was shown in a subsequent paper by the same authors, not to proceed from any diminution in the power of storage of glycogen. In the same child too, between attacks and in the resting condition, the quantity of carbohydrate mobilised from fully replenished stores and oxidised during short periods of fasting was not diminished below the normal. Recently, Haldane⁽⁷⁾ and others have shown that changes in the acid-base balance can profoundly influence carbohydrate metabolism. It is possible that in predisposed children the ketonæmia may have secondary results of this nature.

The Characteristics of the Child with Cyclical Vomiting.

Further investigations in this direction upon the metabolism of normal children and of children with cyclical vomiting are needed before we can have complete understanding of a variety of very common disturbances of health in young children. Nevertheless, what has been already accomplished, although it touches but the fringe of the subject, is so suggestive that it may be profitable to review our clinical studies and concepts in the light of these new findings.

As has been said, all children, just because they are children, respond to a variety of stresses—to infection, to excitement, to over exertion, or to starvation—by the development of ketonæmia. In the child prone to Cyclical Vomiting it is clear that this response is of maximal intensity. Such children, often if not invariably, have certain temperamental and certain physical peculiarities which render their immediate recognition not at all difficult. In general they are the offspring of an intellectual and nervously sensitive stock in which the evidence of other disturbances of metabolism—gout, asthma, and especially migraine—is not wanting. Quick, eager and vital, intensely aware of and interested in their surroundings, the children are prone to exhaust their meagre little bodies by the energy they throw into the whole business of life. There

is generally little doubt about their cleverness although their conspicuous lack of concentration and of dogged perseverance, their restlessness and their irritability may prevent success in school life.

The symptom of which complaint is most usually made is their liability to sudden "turns" or "attacks" or "bouts," as the mother may phrase it. They seem to have an inveterate tendency to fall suddenly and unexpectedly from a height of well being to a level which is very much lower. In the most typical cases these recurrent attacks culminate in, and the clinical picture is coloured by, the excessive emesis. But it is quite usual to find that only a few of the attacks have so culminated in vomiting, while often, although nausea is a pretty constant symptom there has never been any vomiting at all. Whether there is actual vomiting or not the complaints remain remarkably stereotyped. In almost the same words mother after mother will refer to such symptoms as great and rapid loss of weight; pallor with puffiness and lividity under the eyes; prostration; muscular laxity and muscular pains; abdominal tenderness and pain, intermittent and usually of short duration; constant yawning or sighing; constipation; foul smelling breath; excessive perspiration and breathlessness on exertion; giddiness or faintness on rising in the morning; a persistent irregularity of the temperature chart.

In a child of this inheritance, with a high but unstable metabolism, attacks such as those described above may be produced by three sets of causes.

(1) *By undue excitement.* Thus a child who had been to a theatre and had to be taken home, vomiting and collapsed, was found to have very extreme ketonuria.

(2) *By undue exertion.* It is a very usual complaint that these children are unable to travel by train or in a closed motor car. Ketonuria and a low blood sugar have been found in many cases of train sickness in childhood.

(3) *By infection.* It is this last factor of infection which has to be very carefully considered because of the confusion in the clinical picture which is thereby induced. In this particular child whom we are now considering an infection of whatever nature—a common cold for example which runs through a whole household, an attack of tonsillitis or of appendicitis or of pyelitis—will be as it were camouflaged. The well recognised and familiar symptoms of the "attack" are at once in evidence and may completely obscure, if we are not careful, the evidence of the underlying infection. There is considerable risk in such a child for example that an attack of appendicitis may for long pass unrecognised because the illness is presumed to be an uncomplicated attack of the well-known sickness. Close observation should prevent such mistakes. The new and uncontrollable factor of infection is apt to deflect and generally prolong the familiar outline of the attack. In practice, as might be expected, the recurrence of the attack is often determined by the existence of persistent sepsis in the nasopharynx. On the other hand in many cases it is very clear that a catarrhal reaction in the mucous membranes—especially stomatitis, mucous colitis, anal and vaginal irritation, curious white

scaly patches on the skin of the cheeks, cracking of the lips, heralds or accompanies an attack and is a result of the metabolic disturbance not a cause of it. It may be worth while to consider a little in detail from the clinical point of view of a few of the more important symptoms enumerated, such as amyotonia, vasomotor instability, abdominal pain, irregular pyrexia, and the cyclical character of the disturbance.

Amyotonia.

Postural defects, because of the striking tonelessness of the whole muscular system, are commonly found. The whole body droops and sags. Instead of being braced by strong muscular support, the body when upright is balanced in the position of least resistance. The normal postural curves of the spine are greatly exaggerated. To balance the weight over the stance, the shoulders are carried far backwards, and the resulting lordosis throws the abdomen into undue prominence. A secondary compensatory curve in the cervical region is necessary to bring the eyes into line. The weight of the dependent arms bring the shoulders forward and everts the vertebral borders of the scapulæ. The feet are apt to be flat, the knees a little hyperextended. The child tends to lean against any support which offers—his mother, a table, the wall. His power of making that sudden movement of recovery, which may be necessary to prevent a fall is very defective. A slight push may be all that is necessary to upset his balance. Prolonged standing or walking readily produces fatigue. The child is apt to make frequent complaints of transient pains in the muscles of leg, back or shoulders, a complaint which sometimes arouses groundless fears of subacute rheumatism. Postural albuminuria is very common.

Vasomotor Instability.

Together with this amyotonia of the muscles of abdomen, back and limbs, there invariably goes a certain weakness of the vasomotor tone. Thus complaint is almost always made of the pallor of the face and of the dark-rimmed eyes. During exertion or during excitement the face may flush readily, but in the reaction afterwards the pallor is often extreme. In children who have a fixed colour in the cheeks the change may show only around the mouth and eyes. The exercise tolerance is usually low, and breathlessness, with tumultuous action of the heart, is readily provoked by prolonged exertion. Extra systoles and functional heart murmurs are common. Syncopal attacks in older children are not rare. A diagnosis of dilatation of the heart is often made and prolonged rest in bed ordered, or because of aches and pains in the limbs, together with cardiac murmurs and cardiac irregularity, confusion arises with subacute rheumatism, with the same result that prolonged rest in bed is ordered. Yet I think that no type of child stands being bedridden so badly. Lack of tone in the skeletal and in the vasomotor muscles is increased by prolonged confinement to bed, so that the children when at length they are allowed to get up again, tend to show a veritable bed ataxia, with great inco-ordination in movement, giddiness and perhaps fainting.

Abdominal Pain.

Co-incidentally with the attacks of pallor there is apt to be complaint of epigastric pain and discomfort. Such pains are as a rule transient, lasting perhaps but half-an-hour at most, and are often relieved by warmth, by lying down, or by any measure which improves the skin circulation. They are apt to be induced by fright as by a visit to the doctor, by exhaustion, and by the long day spent in the upright position. When seen during an attack of pain there is often considerable abdominal tenderness—sufficient apparently at times to lead the surgeon to remove the vermiform appendix.

Irregular Pyrexia.

Lastly, and this very greatly adds to the difficulty of diagnosis, it is characteristic of these children that the curve of the temperature, taken as is commonly done morning and evening, shows wide divergence from the normal. The so-called monothermia of health seems dependant upon the efficiency of the vasomotor tone. It is true that close inspection of the chart will often show that the subnormal readings are quite as frequent and quite as considerable as those above the normal. Nevertheless, the evening rise of temperature is a frequent cause of anxiety. The aspect of these thin and fragile-looking children whom nothing will fatten is apt to rouse the fear of tuberculosis in the minds of parents, which the evening rise of temperature seems to confirm, nor is it difficult to add further evidence in the shape of an X-ray examination of root shadows of the lung and a positive von Pirquet test. I admit the difficulty of arriving at a right decision in every case, but I feel that in general a diagnosis of tuberculosis must be based on more definite evidence than this. Sometimes indeed the level of the temperature curve is definitely raised for weeks or even months at a time. In such cases a fall to normal can often be achieved by cutting down considerably the intake of food. Dr. Eustace Smith indeed was accustomed to speak of this form of pyrexia as "Food Fever."

The Cyclical Character of the Disturbance.

Amyotonia with transient muscular pains, vasomotor pallor, and cardiovascular weakness, with abdominal pain or discomfort, and irregular pyrexia, are perhaps the most common symptoms. Constipation is the rule; headache and giddiness only occasional complaints. But through all there runs the story of the tendency to live, as it were, on a curve with sudden bouts of prostration and perhaps of vomiting. In many, indeed, the vomiting is by far the most prominent and most distressing symptom. Suddenly, or perhaps after a short prodromal period, marked it may be by pallor, prostration, much yawning and refusal of food, the vomiting begins. While the vomiting is at its height, acetone is generally detected in the breath and in the urine, but its presence in great amounts often follows and does not precede the vomiting. We still lack figures which show quantitatively the output of acetone bodies in children such as I have described during the mild or abortive attacks not culminating or only occasionally culminating in severe vomiting. Langstein and Meyer⁽⁸⁾

have shown that in children the greater part of the acetone bodies are excreted in the breath and not in the urine in which alone detection or estimation is clinically easy.

Whether the attacks are mild or severe, whether with or without actual vomiting, they tend to repeat themselves monotonously, with a strong resemblance one to the other. Sometimes they are preceded by a period of almost exaggerated well-being, when the eye is at its brightest, the energy and appetite of the child apparently greatest. Many mothers have remarked that they have come to dread overhearing their friends congratulate them on the apparent improvement in the child's health, because they have learnt that such congratulations usually herald one of the inexplicable "attacks."

Disturbances of Metabolism, Infection and Nervous Unrest.

That the child with an unstable nervous system has a relatively unstable metabolism may perhaps be taken for granted. That faults of management which produce restlessness, irritation and outbursts of temper, increase this instability of metabolism seems to me clear. Nevertheless, the reverse is also true and the metabolic disturbance is not without influence in producing the symptoms of nervous unrest. It is during the attack of prostration and pallor that the "contrary" child becomes most "contrary," that the timid becomes most timid, the miserable most miserable. At those times lessons usually easily mastered may become far beyond the child's powers. If it is true that the nervous unrest provokes the metabolic crisis, it is equally true that the metabolic crisis may provoke or perpetuate nervous unrest.

No doubt both ketonæmia and hypoglycæmia may be present in the great majority of children without any very visible disturbance of health, yet I think it may be said that, given a certain temperamental and metabolic inheritance, we may recognise a type of child in whom not only are ketonæmia and hypoglycæmia relatively easily produced, but the reaction to these disturbances is characteristic and of the nature described. In such cases it is always worth while to investigate the therapeutic results of an antiketogenic diet prescribed for some weeks, and to combine the relatively high intake of sugar with the daily administration of an alkaline aperatif. Especially when the element of chronic infection is absent improvement may be very striking. It must be remembered that the child depicted above—lax, pale and exhausted—is often a notable cold-catcher with a low immunity against catarrhal infections of all sorts. With improvement in colour, energy, muscle tone, and capacity for exercise, resistance against infection is increased. It is often a difficult task to separate the infective from the metabolic component in the child's illness, and to decide which has played the primary part and which the secondary. Infection is often a cause of the metabolic disturbance, sometimes a result.

To recognise in a child a condition of ketonæmia is not, of course, to achieve a complete diagnosis. The condition is but an extreme reaction in a particular

type of child to various stresses, and most frequently of all to underlying infection. The particular nature and site of the infection often remains to be determined.

Cyclical vomiting, even in its most fully developed form, is a disturbance by no means rarely encountered among the children of the well-to-do. If we include all these milder cases in which the symptoms stop short, as it were, at a lower stage of development and do not culminate in vomiting, the disturbance becomes of every-day occurrence. The study of a diathesis presents this difficulty—that the severe cases on which all would be agreed are separated from the normal by every possible gradation, and there is danger lest the enthusiast discovers its traces everywhere.

In treatment we have to consider at once the parts played by infection, by diet, and perhaps above all by management. When busy, happy and occupied, these difficult little people thrive and are often free from attacks. With unsuccessful management the negativism, the irritability, the restlessness, and the lack of emotional control, lead directly to exhaustion, and provoke the metabolic disturbance which culminates in the disastrous attack.

As with asthma, epilepsy, migraine and many other allied cyclical disturbances, one has the feeling that each attack predisposes to a recurrence, while a long period of immunity seems to increase resistance so that a relapse is only occasioned by a much greater stimulus.

If perhaps in this address I have occupied time with many matters that seem somewhat trifling and have passed a long way from those laboratory studies with which I began, I have the feeling that you will forgive me, because of all that we have learned from the teachings of Sir James Mackenzie, that which seems to me most true and most fundamental is the recognition of the importance for each one of us, in our little way, and in the measure of our opportunities, to busy ourselves in studying the trifling beginnings of ill-health.

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