An Address

ON

SO-CALLED ACIDOSIS IN CHILDREN *

BY

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My subject has been suggested to me by a note which I received last autumn from the head of a preparatory boarding school. It ran: "All my children have returned to school this term suffering from 'acidosis': what is this new disease?" At the present time this is an awkward question. Used as it now is in innumerable children without any obvious discrimination, what is meant by the term "acidosis"? Is it in fact a disease, or a disorder, or a syndrome: is it a clinical diagnosis or merely a biochemical label? At one time the term "acidosis" was kept for a biochemical state, and the phrase "acid intoxication" was used to denote the clinical condition arising therefrom; and if this distinction has now unfortunately lapsed, we must be certain that the symptoms we describe as "acidosis" are not only associated with, but are actually the expression of, the altered blood state.

As I understand it, this modern type of acidosis, which is being recognized in such numbers of children as to tempt us to call it for the moment the pandemic type, derives from the study of cyclical vomiting and other acute forms in which acidosis is present. It is, or at all events it was originally meant to be, the condition of the child prone to cyclical vomiting in between its attacks, the persistent state predisposing to such acute attacks. In order to unravel this rather complicated subject it seems best first to sketch the story of the recognition of the more obvious acute cases, of which so-called cyclical vomiting is the type; secondly, to trace the evolution of the idea of the modern or pandemic type; and lastly to endeavour to draw conclusions on the whole question.

ACUTE TYPE: CYCLICAL VOMITING

The starting-point of the subject of cyclical vomiting is S. Gee's paper entitled "On Fitful or Recurrent Vomiting," published in 1882.¹ This very brief article consists of the notes of nine cases, preceded by an introduction of under 500 words, which opens with the sentence: "These cases seem to be all of the same kind, their characteristic being fits of vomiting, which recur after intervals of uncertain length." It will be seen, therefore, that Gee did not recognize any element of periodicity about the attacks, such as the term cyclical was meant at first to connote; nor did he recognize the presence of acetonæmia. He did, however, specially mention the occurrence of pale stools as one of the features of some attacks. Later the condition was re-described, apparently independently, in America and, I think, in France and Germany.

The association of acetonæmia with this type of case came much later, although the occurrence of β -oxybutyric acid in diabetic urine was known as early as 1884, and acetonæmia many years before that (W. Osler²). I mention this because it is probable that in those days the clinical symptoms of acidosis were regarded as those of diabetic coma, which has little resemblance to an attack of cyclical vomiting. Thus Griffith³ in America

writing on "Recurrent Vomiting in Children (Cyclical Vomiting)" stated: "Acetonæmia may occur, but acetone cannot be considered the poison which produces recurrent vomiting, since the symptoms of acetonæmia are not such as these cases exhibit." L. E. Holt⁴ credits D. L. Edsall⁵ with being the first to emphasize the importance of the acetonæmic symptoms in cyclical vomiting. From that time the view was put forward that in cyclical vomiting there developed an acidosis of unknown origin (cryptogenic acid intoxication, it was called), and that the symptoms of the attack were explained by, and were due to, the presence of this acetonæmia. This view was never universally accepted, for there have always been those who regarded the acetonæmia as a secondary development, the result and not the cause of the symptoms of cyclical vomiting.

In the meantime, L. G. Guthrie⁶ (1894) described the condition which became known as "delayed chloroform poisoning" and later as "post-anaesthetic poisoning." He did not recognize the presence of acetonæmia, but he called attention to the extraordinary degree of fatty disease of the liver found in his fatal cases; and he connected the death with the condition of the liver, suspecting some toxæmia, probably from the intestine, upsetting an already diseased liver. Six years later the first necropsy on a case of cyclical vomiting was reported in America by Griffith,³ and in 1905 the first English necropsy was reported by F. S. Langmead⁷; in both of these advanced fatty change was found in the liver. It was, I think, Langmead (who had in the meantime described the acetonæmia of salicylate poisoning⁸) who first emphasized the striking similarity in the condition of the liver in cyclical vomiting and post-anaesthetic poisoning.⁹ He regarded both disorders as examples of acidosis of unknown origin. This pathological connexion between the two groups of cases is of importance. It was at first a matter of debate whether in cyclical vomiting the changes in the liver were mainly primary or merely the result of the vomiting; but the occurrence of the same peculiar changes after the administration of a known liver poison like chloroform supports the idea that, as Guthrie thought, some toxic action on the liver is the primary cause of the symptoms.

It has been already stated that Edsall's view, that the symptoms of an attack of cyclical vomiting were merely the results of the ketosis, was never universally accepted. Even in the early days it was recognized that there were many points against such an hypothesis, such as the dissimilarity between cyclical vomiting and diabetic coma; the occurrence of acetonuria in a great number of children free of any symptoms; the rapid supervention of acidosis and ketosis in conditions of starvation, and its development as a secondary phenomenon in meningitis, pneumonia, and other diseases ushered in by vomiting. In 1911 E. Mellanby¹⁰ published very careful observations on a case of cyclical vomiting, and was unable to make the occurrence of acetonæmia coincide with the onset or offset of the symptoms, and he expressed the view that "acidosis may probably be disregarded as a cause of any abnormality in any disease, except, it may be, in diabetes."

Of late years further evidence against Edsall's view has accumulated. By means of ketogenic diets it has been possible to produce a marked ketosis in children, yet no symptoms develop. L. Findlay¹¹ has recorded that "even in a case suffering from a mild attack of cyclical vomiting the institution of a ketogenic diet did not interrupt a steady and rapid recovery." A recent review of this subject by J. C. Spence¹² regards the vomiting and drowsiness of cyclical vomiting as due to a recurrent toxæmia, and the ketosis provoked as an

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epiphenomenon. On the other hand, it must be admitted that the sign of hyperpnoea (the air-hunger of Kussmaul) is due to acidosis.

CHRONIC "PANDEMIC" TYPE

Passing to the modern conception of the acidosis child it is clear that it is coloured by the idea of a tendency to ketosis. In the fourth edition of his book on *The Nervous Child*, the first edition to contain a chapter on "The underlying disturbance of metabolism in the nervous child," H. C. Cameron¹³ wrote: "The condition, commonly called acidosis, is therefore more strictly a ketosis, because, although ketosis is a form of acidosis, yet it is one only of the many varieties of acidosis." This was published in 1929, and the next year A. A. Osman tells us of the history of the discovery of this type of case. Writing with H. G. Close,¹⁴ he states that seven years previously, when collecting cases of cyclical vomiting for investigation in the Children's Department at Guy's Hospital, he had observed:

"that those children who had been given extract of malt, largely with the object of securing regular attendance as out-patients, ceased to have further attacks of the disorder. This at once suggested that sugar in some form was the needed antidote. It became apparent, too, that not only was cyclical vomiting easily prevented by this simple and harmless measure, but that a large number of the other common symptoms of debility in children, such as headaches, recurrent abdominal pains, constipation, "growing pains," pallor, and undue fatigability, were also cured and prevented, and that the giving of extra sugar, in any form, quite frequently resulted in a rapid and marked improvement in the general health, spirits, and appearance of the child. In fact, without any other form of treatment, or alteration in the daily regime, a pale, dispirited, ailing child would often be converted into a high-spirited, healthy, and happy being."

Now the first conclusion which Osman draws from his investigations is that "the state of subnormal health in children, usually called 'debility,' is generally associated with some degree of 'acidosis,' defining this as a reduction of the plasma bicarbonate only." But before discussing this, attention must be paid to the significance of the terms as he uses them.

No one will quarrel with the definition of the term "acidosis," but it should be noticed that it does not imply an associated ketosis. Osman found acetonæmia to be quite exceptional in his subnormal children, and indeed the average plasma bicarbonate in the acetonuric children was even a little higher than the average for the plasma bicarbonate in the subnormal group. But it is difficult to understand the point of his paper unless we are meant to infer that acidosis thus defined predisposes a child to ketosis, and we are told that cyclical vomiting occurred in one-third of the normal children investigated but in one-half of the subnormal group with acidosis. Under the name of cyclical vomiting Osman includes not only cases of recurrent attacks of sickness, but also of diarrhoea and of pyrexia, and each of these three forms may occur singly or together. I have already quoted the list of symptoms which he finds so benefited by the administration of sugar, and mention here that he discusses the propriety of adding to them asthma and lowered resistance to infection, while train-sickness and bed-wetting are vaguely mentioned in the clinical notes of his cases.

We are now in a position to discuss Osman's contentions, and to attempt to form an opinion on his proofs of the presence of an acidosis in subnormal children, and more particularly of its clinical significance. His plan of argument in support of the presence of an acidosis is very simply conceived. He took two groups of children, one

consisting of thirty-eight normal children and the other of seventy subnormal or debilitated children, found the value of the plasma bicarbonate readings in each child, and presented an average reading for each group. The figures worked out at 0.0299M as the average for the normal group, and 0.0276M for the subnormal group. Now these figures are average figures, and if we are going to admit the presentation of average figures as a reliable guide, we should wish at least for a considerable difference between one average and the other; here the difference is small. The readings were obtained by an unusual but accepted titration method, and I have not been able to find any standard figures by this method for comparison; but it must be pointed out that the average figure for the subnormal group (0.0276M), although lower than that for the normal group, is well within the range of readings in the individual normal cases (0.0263-0.0321M). I cannot therefore see that Osman has proved beyond dispute the presence of a biochemical acidosis in these cases. But if it is present, what proofs are there that it is of clinical significance? Osman does not give any figures showing that this type of acidosis varies in connexion with vomiting attacks, or that the administration of sugar alters it in any individual cases. We are left to infer that it is connected in some way with cyclical vomiting because this disorder was rather more common in the acidosis group than in the normal group of children investigated, and the good effects were attributed to the administration of sugar. That the type of child who suffers from vomiting attacks can justly be labelled as subnormal has long been known, and is no proof of the effect of acidosis. The arguments based on the effects of glucose therapy I shall consider later.

H. C. Cameron, whose forceful writings on this subject have been so widely read, bases his teaching more on clinical experience than on biochemical investigations. In his new book,¹⁵ published this year, he still alludes to cyclical vomiting as "acetonæmic vomiting," and still regards the acidosis child as one showing latent or overt ketosis. The treatment adopted is designed on this hypothesis, and its success is used to prove the truth of this view. There has, perhaps, been some change in the balance of emphasis, and more stress (as it seems to me) is now laid on the lowered carbohydrate reserve in these acidosis children, which Cameron has called glycopenia.

This is an important point. Doubtless it was first put forward to explain the alleged tendency to ketosis. H. Josephts¹⁶ described recurrent vomiting as "spontaneous hypoglycaemia in children." Osman, however, failed to find any evidence of hypoglycaemia, and, although he admits that this does not exclude the possibility of a diminished glycogen reserve in the liver and elsewhere, strongly deprecates the use of the term glycopenia. Many recent authors have agreed on the probability of a diminished glycogen reserve in the liver, and indeed it is hardly possible to study the debilitated child and its easy fatigability without being sure that this is so. For this condition of diminished glycogen store without actual hypoglycaemia, Cameron's term of glycopenia seems (as is to be expected) both neat and appropriate. On the significance of this glycopenia I comment later.

DISCUSSION

Now let us see if we can piece together these disjointed facts and make something coherent of them. Our dilemma is obvious. While it was believed that these so-called acidosis children were always on the verge of acetonæmia, and that when the attack came, even though its exciting cause were obscure, it was no more than an

exacerbation of a chronic ketosis, the remedy of giving sugar and alkalis and of withholding fats was all in order. But now that it is clear that the marked ketosis is the result and not the cause of the vomiting attacks, and that between attacks there is no ketosis nor any other form of acidosis worth considering, we are left in the peculiar position of having a remedy with, so to speak, no malady attached to it.

My own study of these cyclical vomiting and acidosis children, so-called, leads me to certain conclusions which I will put before you. In the first place, I believe that definite organic conditions are responsible for a much larger proportion of the cases than is generally recognized. Chronic disease of the appendix (which many deny to be possible in children) is not uncommonly to be found, and other conditions worth bearing in mind are atonic dilatation of the stomach and such rarer lesions as partial obstruction due to congenital duodenal ileus. But, setting these aside and dealing only with cases in which the origin of the disorder may justly be called obscure, I believe that there are three factors at work. All these have been noted by various writers on the subject, but two of them have been overshadowed by acidosis views, and the third, as I think, at least partially misinterpreted. They are: (1) intense poisoning of the liver, (2) intestinal toxæmia, and (3) lowered glycogen reserve.

Intense Poisoning of the Liver.—This was noted by Gee in his original paper. The occurrence of pale stools in the attack was one of its features, and many authors agree that this factor is important. The fatty degeneration of the liver found post mortem, so extreme as to be comparable only to that found in post-anaesthetic vomiting, is surely sufficient proof of the importance of this factor. It is to this that the onset of the attack may be attributed.

Intestinal Toxæmia.—The presence of intestinal toxæmia is to my mind incontestable, and has again been emphasized by many writers on the subject. I quite agree with Osman that cyclical vomiting is not particularly associated in between attacks with acetoneuria, but I would point out, as others have done before me, that it is particularly associated with indicanuria, and careful investigation will show the other signs of intestinal indigestion and toxæmia—the enlarged abdomen, the passage of mucus in the stools, and the occurrence, either persistently or occasionally, of foul undigested stools, and so on. I claim that the writings of Osman and Cameron are not only in consonance with this view, but are hardly explicable on any other hypothesis. When we find that cyclical vomiting may consist of recurrent attacks of diarrhoea or bouts of pyrexia with no vomiting at all, what does it mean? When we read Cameron's description of the acidosis child, with its pallid face, coated tongue, ringed eyes, foul breath, bad appetite, and abdominal pains, and when we remember that this condition persists for months or years, how can we believe that this is a picture of mere fatigue, however nervous the child? It is without doubt the picture of fatigue induced and kept up by toxæmia. And since the toxæmia is not a ketosis and is acting in chief on the liver, it is clear that the explanation of the "obscure" case is intestinal toxæmia. It is a curious thing that in the writings of these authors on acidosis in children there is no serious study of the condition of the stools, nor even mention of the prevalence of indicanuria and its increase with the exacerbations of the symptoms.

Lowered Glycogen Reserve.—In the absence of hypoglycaemia there is no satisfactory method of proving a diminished glycogen reserve in the liver; yet it is difficult, on clinical grounds, not to suspect this condition in these children, and we may readily accept Cameron's description

of them as glycopenic if the term is used in this sense. The success that was claimed for glucose therapy was attributed to the prevention of ketosis; but since this explanation is no longer acceptable, it may be suggested that the administration of sugar is of use in rendering the liver less susceptible to poisons brought to it from the alimentary tract. It is established that a liver containing a supply of glycogen is less vulnerable to poisons than one which is depleted; and this hypothesis accounts for the facts that attacks follow not only digestive upsets, which increase the dose of poison carried to the liver, but also periods of excitement or emotionalism, which may be taken to deplete further the glycogen reserve in the liver, and render it temporarily more vulnerable to the intestinal poison. In addition, sugar is, of course, a good food and a mild laxative. If it is objected that this explanation is rather slight to cover the good effects of glucose therapy, I can only say that in my opinion these benefits have been greatly overrated. In my experience in the very numerous instances where the intestinal toxæmia is at all profound, glucose therapy is a complete failure, and prolonged treatment directed towards the improvement of the intestine itself is essential before cure results. As to the other line of treatment advocated, the reduction in the intake of fat, except that it prevents a child from being grossly overfed with fats, I believe it to be unnecessary. I would go further, and say that in my experience this course pursued over many months is definitely harmful.

SUMMARY

In the difficult and complex problem of the cases passing under the names of cyclical vomiting and acidosis, it seems that we must no longer invoke a ketosis as the cause of the symptoms. In acute phases it is a result and not the cause of the attack, and in the interim stages it is not notably present. The exciting cause of the attack is an acute poisoning of the liver, shown by the frequent occurrence of pale stools and the results of necropsies, and the predisposing causes are probably a diminished glycogen reserve in the liver, rendering that organ vulnerable to poisons, and certainly an intestinal toxæmia, persistent with exacerbations. In mild cases the administration of glucose is of help, probably acting by protecting the liver against the effect of toxic absorption from the intestine, but in severer cases patient treatment of the intestine itself is necessary for cure. The withholding of normal supplies of fat in the diet is unnecessary and may be harmful.

It would be a benefit to revise our present terminology. The phrase "cyclical vomiting" has clearly outlived its usefulness, and the term "acidosis," never a happy one for a clinical condition, can hardly, in the light of recent knowledge, be regarded as appropriate.

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