KETONÆMIA AND KETONURIA IN CHILDHOOD.

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The formation of ketone bodies and their excretion in the urine in abnormal amounts have for many years been problems of much interest to both physiologist and clinician. Much of our present knowledge of the subject has been gained from the study of carbohydrate metabolism in diabetes, where ketonuria in its classical form is frequently observed. From this it has been established that an excess of ketone bodies occurs in the blood when the fats are incompletely 'combusted' as a result of abnormal carbohydrate metabolism, and ample justification has been provided for the well-known statement made by Rosenfeld⁽¹⁾ in 1895 'that fat burns only in the fire of carbohydrate.'

A good review of our present knowledge of ketone production and its prevention is to be found in Shaffer's recent lecture entitled 'Antiketogenesis, its Mechanism and Significance.'⁽²⁾ A full discussion of the subject in all its aspects is not within the scope of the present communication, but we may quote Shaffer's statement that 'there is to-day no question that ketosis is due to carbohydrate starvation,' and make special reference also to his reminder that the inhibitory effect of carbohydrate on ketone formation depends, not on the mere existence of sufficient glucose, as glucose, in the blood (*cf.* diabetes), but on the presence of a sufficient amount of an oxidation product of glucose which reacts with one of the acetone bodies or its precursors. That ketosis has long been known to occur during fasting supports the view that it is due to the faulty combustion of fats in the absence of carbohydrate; for the first of the body reserves available is fat, which is then burned in the absence of sufficient glucose for its complete oxidation.

I.—THE CLINICAL SIGNIFICANCE OF KETONURIA.

Clinical interest in the subject has recently been stimulated, and a demand for further investigation made, by the fact that the excretion of abnormal amounts of ketone bodies in the urine is a frequent accompaniment of mild infections in childhood. Ketonuria has been found to occur in a fairly large percentage of hospital patients, irrespective of the disease for which they were admitted.

Garland⁽³⁾, for instance, in 734 cases admitted to the children's wards of the Massachusetts General Hospital, found acetonuria in 17·3%, though in only two of these was there definite evidence of acidosis. Howard⁽⁴⁾ found acetone bodies in the

urine in 18% of 171 children examined, and Smith (5) in a survey of 37 cases, reported acetonuria in 13%. Much higher percentages have, however, been published by Holt⁽⁶⁾ in New York and by Frew⁽⁷⁾ in London. The former gives 30 as the percentage of infants who gave evidence of acetone in the urine out of 200 consecutive cases which he examined on admission to hospital; while Frew found that 61·2% of 662 children admitted showed ketonuria.

Our experience confirms the higher percentages of Frew, as in 300 children admitted to the wards of this hospital we have found that acetone bodies were present in the urine of 54·7%.

The frequency with which acetonuria accompanies disease in childhood was probably responsible for the following comment made by Howland and Marriott⁽⁸⁾ in 1915: 'It has been assumed that the acetone bodies are very abnormal and that their presence signifies an unusual complication in the course of the disease, whereas, in many instances, we may liken the mere presence of acetonuria to fever, for it occurs in most of the infectious diseases of childhood with much the same regularity that fever does.' In consequence of this much quoted statement it has come to be recognised that the acetonuria occurring in the diseases of childhood may be of little significance and may require no special treatment. This, however, in no way advances our knowledge of its causation.

Many theories have been propounded to explain the abnormal excretion of ketone bodies, but, broadly speaking, these can be resolved into three main groups as follows:—

(1) That the ketonuria is caused by the effect of fever on the metabolism.

(2) That ketonuria is due to partial deprivation of carbohydrate resulting from temporary anorexia.

(3) That ketonuria is the result of the psychic disturbances associated with admission to hospital wards.

The first of these theories appears to be well supported by the fact that the published figures for the incidence of ketonuria are much higher in febrile patients than in those without fever. Reiche⁽⁹⁾ found that out of 3,200 patients with diphtheria, acetone bodies were present in the urine of 65%. Proskauer⁽¹⁰⁾ found acetone in the urine of 100 scarlet-fever patients at some time during the illness and attributed it to carbohydrate inanition, the result of toxic influences. Holt's⁽⁶⁾ figure of 70% for patients with lobar pneumonia is much higher than that given by him for the series of miscellaneous cases, while Harris⁽¹¹⁾ gives the startling figure of 85% to represent the incidence of ketonuria in scarlet-fever patients and 90% in diphtheria patients, of whom he examined 197 and 96 respectively. Veeder and Johnstone⁽¹²⁾, however, who estimated quantitatively the amount of the acetone bodies in the urine of 41 cases of infectious diseases, concluded that the presence of acetone in 58% was in no way connected with the severity of the infection nor with the degree of fever. They also concluded from further investigation that the decreased intake of food could not wholly explain the increase of acetone bodies in the urine and assumed that psychic influences played a large part in its causation.

It is important to remember that ketone production can result only from the burning of fat in the absence of sufficient carbohydrate, a state of affairs which may come about in any one of the three ways mentioned above. In fact, each of the suggested factors resolves itself into a relative

or absolute carbohydrate deficiency, and the crux of the problem is to determine which of the three possible factors is responsible for producing this.

Fever may cause relative glucose deficiency by too rapid burning of body fat with which even the combustion of normal amounts of carbohydrate is unable to cope. On the other hand, fever may induce an unduly rapid utilisation of the carbohydrate store, causing a temporary insufficiency which may be further accentuated by a diminished carbohydrate intake.

Anorexia without fever may result in carbohydrate starvation, while psychic influences may lead either to reduced carbohydrate intake or to faulty carbohydrate metabolism, which is undoubtedly influenced by the nervous system. Keeping all these facts in view we have tabulated our results according to the presence of fever, and to the age of the children. The latter classification was adopted on the ground that children over two years would be likely to suffer from a greater degree of psychic upset than those under this age, and we hoped by this means to come to some conclusion regarding the importance of the mental strain of admission to hospital as a factor in the production of ketonuria.

TABLE I.

	Number of cases examined.	Number giving a positive test for acetone	Percentage giving a positive test for acetone.
All cases	300	164	54.7
Febrile patients	119	71	59.6
Afebrile patients	180	93	51.7
Patients over 2 years	169	99	58.5
Patients under 2 years	130	65	50.0

The results shown in Table I. do not reveal as great a difference between the febrile and afebrile groups as might have been expected from the figures of other workers already quoted. It is also seen that although children under 2 years of age suffered less frequently from acetonuria, whether they were fevered or not, the difference in percentages is hardly sufficient to support the view that the condition chiefly results from psychic disturbances. Investigation along these lines has therefore, in our hands at least, proved disappointing. To us it appears that, in each patient, any or all of the various factors may play a part in the production of carbohydrate deficiency and the consequent ketonuria.

At the same time we may point out that amongst our patients high continued fever is frequently met with in which no acetonuria appears and it would therefore seem unlikely that fever *per se* exerts a specific action leading

to derangement of carbohydrate metabolism. We have also been able to show that in an afebrile child whose urine was examined every two hours, complete deprivation of food may exist for 24 hours without the appearance of acetone in the urine as demonstrated by Rothera's test. It is evident from these results, and others quoted below, that the ketogenic reaction to carbohydrate deficiency in different children may vary considerably, not only in the rapidity of its production, but also in its severity: yet it is unlikely that the short partial deprivation of carbohydrate experienced by the ailing child is sufficient, of itself, to produce ketonuria to the degree occasionally met with in hospital practice.

From a general survey of all the opinions to be found in the literature it must be admitted that the cause of the abnormal excretion of ketone bodies has been the subject of much speculation, but that little definite information on the point has emerged. The possibilities of making any real advance in our knowledge are small while there remain unsolved the following problems:—First, the relationship of the amount of ketone acids in the blood to their appearance in the urine; secondly, the point beyond which the accumulation of these acids becomes dangerous; and thirdly, the criteria by which a serious may be distinguished from a negligible ketonuria.

II.—THE RELATIONSHIP OF ACIDOSIS TO KETOSIS.

Although much difference of opinion has existed with regard to the limitations of each of these terms (acidosis and ketosis) the accepted view now appears to be that the term acidosis should be applied only to the condition in which there is a definite shift of the acid-base balance of the blood to the acid side beyond the limits of normal variation. That such a change does not readily occur is to be expected from the fact that Nature has very generously provided for considerable variation in acid intake and acid production by the following mechanisms:—

- (1) The excretion of excess CO_2 and volatile acids *via* the lungs.
- (2) Changes in the base-binding properties of the blood cells according to whether the hæmoglobin is oxygenated or reduced.
- (3) Excretion of excess of non-volatile acids by the kidneys.
- (4) The buffer action of the blood salts.

By these four means the actual hydrogen-ion concentration of the body fluids is kept within what are probably very narrow normal limits. Hence acidosis, in the true sense of the term, should only occur when damage to, or relative under-action of, one of these mechanisms is superimposed upon the over-production or over-absorption of acids such as the ketone bodies.

The danger point in ketone production is universally admitted to be the commencement of an acidosis, but much controversy exists as to the best method of detecting the presence of this condition in its early stages. While several reliable methods for the purpose are available to the physiologist, even the simplest of these is in most cases inaccessible to the clinician in his ordinary work. Measurement of the alveolar CO_2 from which the alkalinity of the blood may be calculated, always difficult and doubtfully reliable, is

specially so in the child. Changes in the hydrogen-ion concentration of the blood as demonstrable by the simpler methods now available, can only be obtained in the presence of an acidosis so severe as to be easily recognised clinically. In our hands it has not been possible to demonstrate any marked change in the pH by the method of Dale and Evans⁽¹³⁾, even in cases where all the recognised signs of clinical acidosis were present.

The only practical methods left to us for judging the severity of a ketonæmia are therefore the CO₂-combining power of the blood ('alkaline reserve'), and the actual measurement of the acid suspected to be the cause of the disturbance. It was partly with the object of attempting to show some connection between these two latter factors that the present investigation was undertaken.

By making use of the present knowledge of ketogenesis and anti-ketogenesis it has been found possible to classify the commoner foodstuffs according to their ability to produce or to inhibit the production of ketone acids. Thus each of the proximate principles is known to contain roughly a constant number of ketogenic and antiketogenic units, and a diet containing an excess of ketogenic units can be depended upon to produce an excess of ketone acids in the course of its combustion. Such an acid-producing diet has been employed therapeutically, chiefly in America, for the treatment of epilepsy and an admirable opportunity has thus presented itself for the study of the factors associated with the production of ketone bodies in the blood, their relation to the blood sugar, and their effect on the acid-base balance of the body. It was hoped that the present study would give further confirmation of the results so obtained and throw some light on the responses of ketonæmia to various forms of treatment.

Methods.—The children who were the subjects of investigation were for the most part epileptics of between 6 and 12 years of age. In each case, after a few days on general diet, the alkaline reserve, blood acetone, and blood sugar were determined. The patient was then given a ketogenic diet consisting of fat bacon, butter, cream, and diabetic rolls. By this means 5 grammes of fat and 0.2 grammes of carbohydrate were consumed for every gramme of protein, the proximate principles thus being supplied in the following proportions:—*fat*, 25; *protein*, 5; *carbohydrate*, 1. The actual amounts of each item of diet were varied slightly according to the age of the child but the proportions were in all cases roughly the same. During the experiment all the patients except one were kept at rest in bed, and the diet supplied contained on an average 600 to 700 calories more than the calculated basal requirement. Nevertheless, all the children except two lost weight slightly, though they took the diet well and complained only of the excessive amount of butter which had to be consumed with each roll.

The daily quantities of urine were collected and the total acetone bodies estimated and stated in terms of grammes of acetone per litre. Where possible the amount of urine passed during the 24 hours was accurately measured and the total amount of acetone excreted in the 24 hours calculated. Blood-acetone and alkaline-reserve estimations were made at intervals during the period on the ketogenic diet and in several cases the blood sugar was also estimated. The figures for blood acetone represent the total acetone bodies in grammes of acetone per litre as obtained by the Van Slyke method⁽¹⁴⁾. The alkaline reserve was estimated by means of the Van Slyke⁽¹⁵⁾ apparatus, duplicate estimations being made in each case. MacLean's⁽¹⁶⁾ method was

used for estimating the percentage of sugar in the blood, each estimation being preceded by a fast of at least three hours. After varying periods, treatment for combating the ketonuria was instituted and the behaviour of the acetone in the blood and urine, and of the alkaline reserve watched for a further period of several days.

In all 14 studies were made. Details of the various studies are given in Tables III. to VI., and one result from each class of experiment graphically represented in Charts I. to IV.

DISCUSSION OF RESULTS.

(i.) *Acetone in Blood and Urine.*

Although figures for the concentration of the acetone bodies in normal blood and urine are already available in the literature, we have found it exceedingly difficult to obtain from them an idea of the average normal amount, because the various workers have employed not only different methods, but also different terms for the expression of their final results.

The results collected from the literature are given in the following table:—

TABLE II.

AMOUNT OF BLOOD ACETONE AND URINE ACETONE IN HEALTHY CHILDREN
ACCORDING TO VARIOUS AUTHORS.

Authors	Method	BLOOD: result expressed in mgms. % in terms of			URINE: re- sult expressed in mgms. % in terms of acetone
		Acetone	Acetone & Aceto- acetic acid	Oxybuty- ric acid	
Hubbard and Novack (17)	Modification of Messinger	0 to 0.3	..	...	0 to 1.2
Marriott (18) ...	Modification of Shaffer	0.5 to 15	...	...	...
Veeder and Johnstone (19)	Shaffer...	...	...	...	50 to 80 mgms. per diem
Marfan (20) ...	Not given	...	...	...	30 to 80 mgms. per diem
Jeans and John- stone (21)	Marriott's	10	...	...	...
Moore (22) ...	Marriott's	0.8 to 13	...	...	...
Hubbard (23) ...	Hubbard	...	0.41	0.8	...
Van Slyke (14)...	Van Slyke	1.3 to 2.8	...	...	2.8
Brown & Graham (Present co-m- munication)	Van Slyke	0 to 1.7	...	...	0 to 17

It would appear from the figures given in Table II. that the total acetone bodies of the blood when expressed in mgms per 100 cc. may vary from 0 to 15 (0 to 0.15 grms. per litre).

Marriott's⁽¹⁸⁾ and Moore's⁽²²⁾ results, which were both obtained by the same method, agree very well, and when combined give a normal variation for children of from 0.005 to 0.15 grms. per litre. Our figures obtained by the Van Slyke method showed a much smaller range of variation (0 to 0.017 grms. per litre) in 19 normal children, and are in keeping with the results obtained in adults by the originator of the method. This variation of the results according to the method employed shows the necessity for the establishment by each worker of his own normal figures. From our study we conclude that with the Van Slyke method any figure over 0.020 grms. per litre is abnormally high. It would also seem that individual variations over very prolonged periods are not inconsiderable, for one patient on a general diet showed the following variations in the blood acetone figures from time to time:—

Case No.	November 6th	...	0.006	grms.	per litre.
	„ 24th	...	0.018	„	„ „
	December 3rd	...	0.009	„	„ „

Our results show clearly that the administration of a ketogenic diet causes in every case a rapid increase of the acetone bodies in the blood. In the one patient (Case No. 11) whose blood was examined daily, the rise was apparent after 24 hours on a high fat diet and continued with one negligible remission till the eighth day when it began to show a slight spontaneous fall. This is in accordance with the results in fasting obtained by other workers. Labbé and Nepveux, for example, state that after a maximum period of seven days the acetone bodies tend to disappear spontaneously though the fasting is continued. It would seem, therefore, that after some days the metabolism is able to adjust itself partially to the lack of carbohydrate.

A closer study of all the figures has revealed the fact that a ketogenic diet may produce an increase in the blood acetone of anything from 2 to 40 times the normal amount. For example, Case No. 7 whose blood acetone was 0.001 grms. per litre at the beginning of the experiment had 0.041 grms. per litre on the sixth day of the ketogenic period; while Case No. 1, a child of the same age and on the same diet, began the experiment with 0.015 grms. per litre and on the sixth day had only 0.022 grms. The factors which determine the severity of the reactions to the ketogenic diet are not apparent, but probably are connected in some way with variations in metabolic rate.

When an increase in the blood acetone was obtained, due either to starvation or to a ketogenic diet, the ketonuria was also markedly increased and the figures show a rough parallelism. The correspondence between the figures is not close, yet they seem to justify the general conclusion that increase in the urinary acetone indicates undoubted increase in the blood acetone, though this may be only slight. In none of the cases have acetone

no way limited yet the daily output of urine showed remarkably little variation, considering the marked changes which were apparent in the acetone figures. That acetone differs from other acids in this respect might be explained by its volatility, which renders it capable of excretion by the lungs as well as by the kidneys. No attempt has been made to measure the acetone excretion by the lungs in the present series of cases; but a smell of acetone was perceptible in the breath of only three of our 14 cases, and in these (Nos. 2, 8, and 11), the rise in the acetone of the blood and urine was not as marked as some of the others. The presence of an acetone smell in the breath does not therefore appear to be a reliable criterion of the severity of a ketonæmia.

(ii) *Alkaline Reserve.*

It is strikingly evident from Tables III. to VI. and the charts appended that increase in the acetone bodies of the blood is invariably accompanied by a fall in the alkaline reserve. The nature and degree of the fall was so constant that we were able with some accuracy to predict the behaviour of the plasma-bicarbonate curves in a child who was given a ketogenic diet. A rise in the blood acetone is invariably accompanied by a corresponding fall in the alkaline reserve.

Gamble⁽²⁴⁾ has demonstrated a similar fall in the serum bicarbonate in fasting children and believes the reduction to be directly and wholly due to an increase in the ketone acids. Talbot, Shaw and Moriarty⁽²⁵⁾ give further confirmation of this fall in available alkali with a corresponding rise in acetone production during fasting, and it is only to be expected that a similar result would be obtained by the administration of a ketogenic diet. The degree of reduction in the bicarbonate reserve in the various cases is relatively constant. The range of normal variation in the children under investigation was 55 to 69 vol. per cent., while during the ketogenic period the figures varied between 32.3 and 46.8 vol. per cent. The reduction to these values appeared to occur irrespective of the degree of increase in the acetone content of the blood. It would therefore be incorrect to take any individual reading of the bicarbonate reserve as an indication at that time of the possible level of the blood acetone; but it may be assumed that, where the conditions are favourable for the production of ketone bodies, any reduction in the alkaline reserve indicates a definite increase in the blood acetone.

The point next to be considered is whether the fall in the alkaline reserve under these conditions is to be taken as indicating a change in the acidity of the body fluids. In other words, does reduction in alkaline reserve in ketonæmia mean reduced serum pH and consequent acidosis? In this connection we were struck by the invariable fact that patients were to all appearance quite unaffected by the changes which were undoubtedly taking place in their metabolism. As already stated only three of the cases developed a perceptible smell of acetone in the breath, and in no case was increased rate or depth of respiration clinically evident.

A fall in the alkaline reserve such as that obtained above should theoretically result in a change in the acidity of the body fluid, since the rapid washing out of CO_2 via the lungs by over-ventilation, which would have been necessary to compensate for the reduction in alkali, did not occur. Gamble⁽²⁴⁾ has recently pointed out that, until now, we have been inclined to think that little actual increase in plasma acidity takes place even in the presence of greatly reduced bicarbonate. Direct measurement of plasma pH by Cullen's⁽³⁹⁾ method, however, has shown (*vide* Talbot, Shaw and Moriarty⁽²⁵⁾) that even moderate reduction of bicarbonate may cause a considerable fall in pH. It therefore seems justifiable to assume that, in the absence of a definite increase in CO_2 output by over-ventilation, a reduction in the alkaline reserve must be taken as an indication of a reduction in the serum pH, and consequent acidosis. If we apply this assumption to our own results we must conclude that acidosis (or ketosis in our use of the word) may occur in childhood without giving rise to any clinical manifestation of its presence.

(iii) *Blood Sugar.*

Much work on the value of blood-sugar estimations in acidosis and ketosis has already been done but the results so far available seem contradictory. The earlier workers, *e.g.*, Allen⁽²⁶⁾, state definitely that no fall in the blood sugar takes place even after prolonged fasting. During the past few years, however, this has been contradicted, especially by the American workers, who found a very definite fall in the blood sugar of fasting children. It might be expected that in fasting, where the carbohydrate insufficiency is extreme, a low blood sugar would inevitably follow depletion of the glycogen reserves of the body, but a review of the literature reveals no reference to a low blood sugar after fasting in adults. This does not necessarily mean that such will not occur in children. In them there may be perhaps a more rapid utilisation of the mobilised glucose than in the adult, which would account for the rapid fall in the blood sugar which has been obtained by some of those who have studied fasting children.

Mogwitsch⁽²⁷⁾ in 1914, recorded a lowering of the blood sugar in five fasting children. In one infant, after a fast of 72 hours, he found that the blood sugar, which was '09% three hours after the last feed, had fallen to '047%. Sawyer⁽²⁸⁾, who gave diets of very low caloric value to several children with very variable results, observed in some cases a slight rise in the blood sugar and in one case a very marked fall to '020%, a figure which is hardly compatible with life. Talbot, Shaw and Moriarty⁽²⁵⁾, in eight cases in which they produced a ketosis by fasting, found a marked fall in the blood sugar in all; in some instances figures of '045% and '038% were recorded, but in only one of the cases were there any symptoms of hypoglycæmia. Ross and Joseph⁽²⁹⁾ found a very low blood sugar in one case subject to attacks of cyclical vomiting. As the examination was made between the attacks the lowering noted apparently was not due to vomiting, which we know can give rise to a moderate reduction in the blood sugar values. After a fast of six hours in this case there occurred a fall in the blood sugar from '100% to '086%, while 14 hours later it had reached the low level of '049%. In a series of controls, Ross and Joseph⁽²⁹⁾ obtained only a very slight fall in the blood sugar on the fourth to the fifth day of starvation.

Schlossmann⁽³⁰⁾ found that the blood sugar remained normal till 72 hours after food and then fell sharply. Hoeffel and Moriarty⁽³¹⁾ fasted two cases of epilepsy eight and nine days respectively, and got a marked fall in the blood sugar in both. In the former a fall of from 0.075% to .059% was obtained, while in the latter the fall was more marked, from .100% before the fast to .052% after nine days' fasting. Shaw and Moriarty⁽³²⁾ kept five epileptic children on a fixed diet for three to four days, after which they were fasted for ten to 14 days, only water being given during the period. A fall in the blood sugar coincident with a fall in the alkaline reserve resulted, but towards the end of the fast both the blood sugar and the alkaline reserve tended to rise again. In all of these cases quoted the fall in the blood sugar took place along with the development of a ketonæmia. Where an excess formation of ketone bodies has been produced by the giving of a ketogenic diet, however, this fall in the blood sugar has not been so marked.

Ross and Joseph⁽²⁹⁾, in two children on a high fat and low carbohydrate diet, found a slight fall in the blood sugar coinciding with the increase in the fat-carbohydrate ratio. In the first case the normal fasting blood sugar was .096% and after ten days on a ketogenic diet had fallen to .084%, while in the second case it fell from .112% to .091%.

In the ketosis accompanying infections a high fasting blood sugar has been noted by Tallerman⁽³³⁾, while Chapin and Myers⁽³⁴⁾ found a slight fall in the blood sugar in cases of acidosis (not necessarily ketosis) accompanying gastro-enteritis and malnutrition.

Langfeldt⁽³⁵⁾ in the case of adults, by administering acid either *per os* or intravenously and thus causing an acidosis, states that glycogenolysis takes place followed by hyperglycæmia and glycosuria, and Haldane⁽³⁶⁾ found that though a disturbance of carbohydrate tolerance may result from acidosis, the fasting blood sugar is usually normal. He concluded that acidosis leads to a disturbance of carbohydrate storing and not to a disturbance of its oxidation.

The fasting blood sugar was examined in some of our cases at the beginning of the experiment and also after ketogenic periods of varying duration; as is shown in Tables III to VI and Charts I to IV, no appreciable fall in the blood sugar was obtained. The most marked fall was in Case No. 6, where the normal fasting blood sugar was .106% and after eight days on a ketogenic diet had fallen to .085% and four days later was still at the same level. The absence of any marked alteration in the blood sugar values in this series of cases is difficult to correlate with the theory that excess of ketone acids is the result of relative carbohydrate insufficiency. The type of glucose circulating in the blood was, however, not investigated, and it is recognised that this may be a point of considerable importance, since it is known that all types of glucose are not equally efficient as antiketogenics. The maintenance of a normal blood sugar content can be explained on the assumption that the shift in acid-base balance to the acid side, resulting from the ketonæmia, inhibits the storing of any carbohydrate, and so provides that all the available supply is used to maintain a normal blood sugar. As already stated Haldane⁽³⁶⁾ showed that the production of an acidosis results in a disturbance of the body's capacity to store glucose but not to oxidise it. It therefore seems possible that the accumulation of ketone acids to excess may in itself tend to keep the blood sugar normal by diminishing the amount stored. It is even conceivable that, so long as

storing does not take place, sufficient glucose is available from other sources, such as protein, to maintain the level of the blood sugar even during the administration of an almost entirely carbohydrate-free diet. Further work on the behaviour of the carbohydrate metabolism during ketonæmia is necessary and is at present under consideration.

CHART II.

Case No. 8.—Ketogenic Diet followed by Glucose.

III.—DISAPPEARANCE OF KETONÆMIA AND KETONURIA UNDER VARIOUS FORMS OF TREATMENT.

In order to test the effect of various changes in diet on the ketonæmia and ketonuria the following further studies in the same series of cases were made, when as a result of the ketogenic diet a definite rise in the blood acetone and fall in the alkaline reserve were apparent:—

(a) Five children (Cases Nos. 1-5) were kept on the ketone-producing diet, with in addition the administration of sodium bicarbonate.

(b) Four children (Cases Nos. 6-9) were kept on the ketogenic diet with the addition of glucose.

(c) Four children (Cases Nos. 10-13) were changed from a ketogenic diet to the ordinary diet for children of the same age.

(d) One child (Case No. 14) was kept on the ketogenic diet with the addition of both glucose and sodium bicarbonate.

The effects of these various changes are shown graphically in Charts I to IV.

A comparison of the results obtained in the four groups is interesting. The addition of glucose to the ketogenic diet and the change to the ordinary diet are, as one would expect, similar in their effect. Patients subjected to either of these forms of procedure showed a rapid diminution in the ketonæmia and the ketonuria with a coincident rise in the bicarbonate content of the serum, all three values returning to normal within four days of the commencement of treatment. In no case did recovery result in markedly increased excretion of ketone acid, as the blood and urine acetone fell simultaneously. It was therefore obvious that the effect of the administration of glucose or of an ordinary diet was to arrest the formation of acetone bodies, with a consequent rapid diminution in the amounts retained and excreted.

A further point of interest is that the amount of glucose administered was smaller than that generally recommended to keep the fat-glucose ratio within the antiketogenic border line. The ratio of ketogenic to antiketogenic units in the acid-producing diet was, as calculated from Shaffer's⁽²⁾ data, roughly 3.5 to 1. The addition of 30 grms. of pure glucose *per diem* reduced the ratio to 2 to 1. In spite of the fact that a ratio of 1 to 1 should be necessary for the prevention of ketogenesis the 2 to 1 ratio seemed to be adequate for the reduction of the ketonæmia present in our cases. Whether this was due to the fact that by the time glucose was supplied the body had already attempted adjustment of the metabolism by the conversion of protein into carbohydrate, is not clear as nitrogen output was not estimated, but the results raise a point of considerable importance in the study of ketogenesis.

The addition to the ketogenic diet of sodium bicarbonate in doses of 120 to 180 grains *per diem* gave less uniform results. While two of the cases appeared to return to normal within four days and were not followed further, each of the remaining cases showed some anomaly which we were at a loss to explain. Case 1, for example, whose blood acetone showed unusually little change throughout the whole course of the experiment, presented a distinct rise in the acetone output immediately after the administration of sodium bicarbonate, while at the end of the experiment the ketone percentages in blood and urine were still higher than they had been on a general diet. One other case responded by a steady gradual reduction in the urinary ketone, but with a steady rise in the blood acetone. The only consistent result obtained by the administration of alkali was a return of the bicarbonate reserve to normal or slightly high values. From a

consideration of the factors influencing the production of excess of ketone acids in the body it could hardly be expected that sodium bicarbonate would have as favourable an effect on the ketonæmia as glucose. Nevertheless it seemed possible that the alkali might assist the rapid elimination of ketone acids already produced and so give rise to increased acetone output in the urine and a possible diminution in the degree of ketonæmia. This however proved not to be the case for, where a favourable result was obtained, the urinary values fell along with the blood values.

CHART III.

Case No 11 —Ketogenic Diet followed by Ordinary Diet.

Recent investigations by Haldane⁽³⁶⁾ and by Shaffer⁽²⁾ have shown that changes in the acid-base balance may exert a profound influence on the carbohydrate metabolism. Support for this view has been provided by Ellis⁽³⁷⁾ and by Haldane⁽³⁶⁾, both of whom noted that acetone bodies appear in the urine in alkalæmia and after the consumption of very large doses of sodium bicarbonate. One of us (G. G.) in a former investigation of tetany⁽³⁸⁾ attempted to produce alkalæmia in normal children by the administration of bicarbonate but found that this was merely excreted, and that the alkaline reserve of the plasma remained normal. In order to make

a further test of the administration of alkali on acetone production, sodium bicarbonate, in doses of from 180 to 600 grains in the 24 hours, was given to two children aged 9 and 10 years. According to the formula of Cullen and Austin⁽³⁹⁾ $\frac{38g}{W} \left(\frac{38 \text{ grms. Sod. Bicarb.}}{\text{Weight of Child.}} \right)$ 600 grains daily is ample to produce a marked increase in the plasma bicarbonate. This it entirely failed to do in spite of the fact that one of the subjects for the experiment was a chronic nephritic, whose renal efficiency might have been expected to interfere with alkali excretion. In neither case did acetone appear in the urine up till the fifth day after the administration of the last dose of bicarbonate.

In view of the fact that, as recently stated by Shaffer⁽²⁾, alkali is essential for the complete oxidation of glucose by air or H_2O_2 in vitro, one would expect a quicker return of the blood acetone to normal if glucose and sodium bicarbonate were administered together. In one case where a ketogenic diet had been administered, the effect of this combination of glucose and alkali was tested. It was found, however, that the alkali had no apparent effect, the blood acetone and the urine acetone acting in the same way as when glucose alone was administered. The effect of glucose is therefore to arrest the formation of ketone bodies and so permit of their removal within a few days. The effect of alkali administration on the blood and urine was not constant and could therefore not be depended on, except to produce a rapid return of the alkaline reserve to a normal or even slightly raised figure.

IV.—CONCLUSIONS.

(1) Ketonuria occurred in 54·7% of 300 consecutive cases admitted to the Royal Hospital for Sick Children, Glasgow.

(2) The Van Slyke method gives normal blood acetone values of from 0 to 0·017 grms. per litre in children of 6 to 12 years of age.

(3) An increase in the blood acetone from 2 to 40 times its normal amount occurs on the administration of a ketogenic diet. This rise is accompanied by a fall in the alkaline reserve and an increase in the urinary acetone, but there is no definite reduction in the blood sugar.

(4) In ketonæmia, glucose administration results in rapid diminution of blood and urine acetone, with a corresponding rise in the alkaline reserve.

(5) In ketonæmia the administration of sodium bicarbonate cannot be depended on to reduce the blood and urine acetone, but is beneficial in procuring a rapid return to normal of the low alkaline reserve.

(6) Glucose administration would therefore seem the rational and correct treatment for ketonæmia or ketosis, but sodium bicarbonate would appear to be of use in the immediate relief of any symptoms which may be due to the reduction in the body alkali.

The expenses of this investigation have been defrayed by the Medical Research Council to which we desire to express our gratitude.

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TABLE III.

CASES ON KETOGENIC DIET TREATED WITH BICARBONATE OF SODA.

Case No	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
1.	1	Ordinary Diet	...	·015	61·3	·086
	2	Ketogenic Diet	·188	...	...	...
	3	" " " " " " " " " " " "	·345	...	...	...
	4	" " " " " " " " " " " "	·512	...	...	...
	5	" " " " " " " " " " " "	...	·024	...	·080
	6	" " " " " " " " " " " "	...	·312	...	...
	7	" " " " " " " " " " " "	...	·022	46·8	...
	8	{ Ketogenic Diet + Sod.	·669	...	52·6	·080
	9	{ Bic. gr. xx 4 times	·578	...	...	...
	10	{ Ketogenic Diet + Sod.	·379	·029	46·8	...
	11	{ Bic. gr. xl 4 times	·644	...	59·4	...
2.	1.	Ordinary Diet	...	·017	57·4	·098
	3	Ketogenic Diet	·189	...	...	...
	4	" " " " " " " " " " " "	·536	...	...	...
	5	" " " " " " " " " " " "	·719	·061	32·3	·086
	6	" " " " " " " " " " " "	·724	...	...	...
	7	" " " " " " " " " " " "	·756	·063	52·6	...
	8	{ Ketogenic Diet + Sod.	·784	...	...	...
	9	{ Bic. gr. xxx, 6 times	·668	·029	58	...
	11	" " " " " " " " " " " "	·544	·009	71·9	...
3.	1	Ordinary Diet	·165	·007	55·5	...
	2	Ketogenic Diet	·204	...	...	...
	3	" " " " " " " " " " " "	·194	...	...	...
	4	" " " " " " " " " " " "	·286	...	...	...
	5	" " " " " " " " " " " "	·378	·042	43·9	...
	6	" " " " " " " " " " " "	·406	...	...	...
	7	" " " " " " " " " " " "	·586	·051	36·1	...
	8	{ Ketogenic Diet + Sod.	·516	·027	59·4	...
	9	{ Bic. gr. xx, 6 times	·472	·004	67·1	...
	10	" " " " " " " " " " " "	·254	·012	57·6	...
4	1	Ordinary Diet	...	·006	62·3	...
	3	Ketogenic Diet	·174	...	...	...
	4	" " " " " " " " " " " "	·253	...	...	...
	5	" " " " " " " " " " " "	·372	...	...	...
	6	" " " " " " " " " " " "	·266	...	...	...
	7	" " " " " " " " " " " "	·454	·059	38·1	...
	8	{ Ketogenic Diet + Sod.	·359	...	...	...
	9	{ Bic. gr. xxx, 5 times	·221	·079	62·3	...
	10	" " " " " " " " " " " "	·110	...	...	...
	11	" " " " " " " " " " " "	·093	·126	52·6	...
5.	1	Ordinary Diet	...	·010	42·9	·098
	2	Ketogenic Diet	·018	...	...	...
	3	" " " " " " " " " " " "	·056	...	...	...
	4	" " " " " " " " " " " "	·154	...	...	...
	5	" " " " " " " " " " " "	·071	...	...	...
	6	{ Ketogenic Diet + Sod.	·253	·080	42·9	·088
	7	{ Bic. gr. xxx, 4 times	...	...	...	·094
	8	" " " " " " " " " " " "	·345	...	57·4	...
	9	" " " " " " " " " " " "	·342	...	...	...
	10	Ordinary Diet	·243	·015	68	·100
	11	" " " " " " " " " " " "	·195	...	...	...

TABLE IV.

CASES ON KETOGENIC DIET TREATED WITH GLUCOSE.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grs. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
6.	1	Ordinary Diet	...	·004	69	...
	2	Ketogenic Diet	·012	...	69	·106
	3	" "	·136	...	...	...
	4	" "	·074	...	...	...
	5	" "	·166	...	...	...
	6	" "	·359	...	...	...
	7	" "	·645	·032	41	·094
	8	" "	·553	...	...	...
	9	" "	·386	·087	53·6	·085
	11	" "	·248	·011	60·70	·084
	14	{ Ketogenic Diet + 100 cc. 5 % Glucose 5 times ... }	{ ·823	·034	38	...
	15	" " " "	·818	·042	38	...
	16	" " " "	·513	·065	40	...
	17	" " " "	·595	·051	42·9	·100
7.	1	Ordinary Diet	...	·001	49·7	·094
	3	Ketogenic Diet	·048	...	...	...
	4	" "	·343	...	...	...
	5	" "	·696	...	...	...
	7	" "	1·255	·041	42·9	·098
	8	{ Ketogenic Diet + 100 cc. 5 % Glucose 6 times ... }	{ ·541	...	...	...
	9	" " " "	·581	·003	59·4	...
	10	" " " "	·304	...	...	...
	11	" " " "	·356	·019	57·4	...
	14	" " " "	·043	...	...	...
8.	1	Ordinary Diet	·054	·009	59·4	·106
	4	Ketogenic Diet	·254	·058	42·6	...
	7	" "	·347	·049	46·8	...
	8	{ Ketogenic Diet + 100 cc. 5 % Glucose 5 times ... }	{ ·532	·027	56·5	·100
	9	" " " "	·478	·017	61·4	·100
	10	" " " "	·284	·003	64·2	...
	11	" " " "	·148	·012	64·2	...
9.	1	Ordinary Diet	...	·016	61·3	·100
	3	Ketogenic Diet	·048	...	...	...
	4	" "	·576	...	...	...
	5	" "	1·016	...	...	...
	6	" "	·377	...	...	...
	7	" "	·359	·155	41	·094
	8	{ Ketogenic Diet + 100 cc. 5 % Glucose 6 times ... }	{ ·238	...	...	...
	9	" " " "	·130	·003	53·6	...
	10	" " " "	·083	...	...	...
	11	" " " "	·051	·034	56·4	...
	12	" " " "	·058	...	...	...

TABLE V.

CASES ON KETOGENIC DIET TREATED WITH ORDINARY DIET.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
10.	1	Ordinary Diet	·170	·012	65·2	·100
	2	Ketogenic Diet	·098	...	...	...
	3	" "	·295	·085	44·6	·102
	4	" "	·389	·088	39·1	·098
	5	" "	·570	·084	40	·098
	6	" "	·440	...	...	...
	7	Ordinary Diet	·256	·054	...	...
	8	" "	·106	...	...	...
	9	" "	·125	·0078	69	·106
11.	1	" "	·019	·0064	55·5	·098
	2	Ketogenic Diet	·148	·018	59·4	...
	3	" "	·298	·015	45·6	...
	4	" "	·346	·044	42	...
	5	" "	·489	·054	...	...
	7	" "	·456	·047	46·5	...
	8	" "	·523	...	...	...
	9	" "	·498	·043	36·1	...
	10	Ordinary Diet	·518	·031	...	...
	11	" "	·527	...	...	...
	12	" "	·524	·033	65·2	...
	16	" "	·298	·025	59·2	...
	17	" "	·198	...	...	...
12.	2	Ketogenic Diet	·272	...	...	...
	3	" "	·372	...	...	...
	4	" "	·346	...	...	·090
	5	" "	·412	...	...	...
	6	" "	·416	·051	45·8	...
	7	Ordinary Diet	·541	·034	48·7	...
	8	" "	·382	·009	62·5	·100
	9	" "	·339	...	...	...
	10	" "	·192	·012	64·2	...
	11	" "	·204	...	...	...
13.	1	" "	·098	·064	62	...
	6	Starvation Diet	·409	·037	40	·090
	7	" "	·553	...	...	·096
	8	" "	·434	...	...	·086
	9	" "	·540	·045	40	·094
	10	Ordinary Diet	·267	...	...	...
	11	" "	·277	...	...	...
	12	" "	·099	·009	64·2	·099
	13	" "	·122	...	...	·096

TABLE VI.

CASES ON KETOGENIC DIET TREATED WITH GLUCOSE AND BICARBONATE OF SODA.

Case No.	Days of Investigation.	Diet and Treatment.	Acetone in Urine in grms. per litre.	Acetone in Blood in grms. per litre.	Alkaline Reserve. Vol. per cent.	Percentage of Blood Sugar.
14.	1	Ketogenic Diet	...	...	...	...
	2	" "	149	...	...	106
	3	" "	325	...	...	...
	6	" "	488	042	58	...
	7	Ketogenic Diet + Sod. Bic. gr. xxx, 100cc. 5 % Glucose 5 times	512	038	55.5	100
	8		453	012	...	...
	9		209	...	...	...
	10		126	...	...	...

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CHART IV.

Case No. 14.—Ketogenic Diet followed by Glucose and Sod. Bicarbonate.