GLYCOSURIA IN CHILDHOOD.†

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Glycosuria although not in itself serious is of the utmost importance as a diagnostic clue to a metabolic defect which may or may not be of grave import. In the majority of cases the onset of diabetes mellitus in childhood is heralded by the symptoms of thirst and polyuria: thus in 30 cases of diabetes at the Royal Hospital for Sick Children, Glasgow, thirst was a first manifestation in 27 and polyuria in 23. Nevertheless, there exists a certain number in whom the onset of glycosuria is silent so that in the routine examination of children it is of importance not to neglect the urinary tests which in children are so apt to be overlooked. It must, however, be emphasized that although glycosuria associated with polyuria and thirst is almost invariably due to diabetes, silent glycosuria is frequently not of the same grave significance. Holst has followed the subsequent histories of 150 persons who were refused life insurance because of glycosuria: he found that over periods varying from 5 to 16 years only 30 exhibited the clinical picture of true diabetes mellitus. It is clear, therefore, that the correct interpretation of "silent" glycosuria presents a problem of great practical importance to the patient.

The common tests for glycosuria are Fehling's and Benedict's. The latter is rather the more delicate of the two but not sufficiently so to detect the small amount of sugar which is present in normal urine. It may be as well to point out that Benedict's test as performed with the qualitative reagent is definitely positive only when the precipitate is yellow or red: a white or whitish grey precipitate is due to phosphates. Even with this precaution it is important to remember that there are substances other than glucose which give a positive test with Benedict's or Fehling's reagents. If a preservative has to be used chloroform and formaline should be avoided since both are reducing agents. Uric acid and creatinine in excess, glycuronates derived from antipyrine, camphor, chloral, morphia, etc., salicyluric acid from salicylates, and homogentisic acid (alkaptonuria) all may give a positive test. Of the sugars glucose, lævulose, galactose, lactose and pentose reduce Fehling's and Benedict's reagents. In a case of doubt the yeast fermentation test is the best; it is positive only in the presence of glucose and lævulose: these two sugars may be differentiated by their action on polarised light. Galactose which ferments slowly with yeast is a very rare constituent of urine.

Incidentally the presence in the urine of sugars other than glucose is not of serious import. It has been stated that lævulosuria is indicative of hepatic inefficiency but the evidence for such a view is not very strong. Chronic lævulosuria can be cured by withdrawing cane-sugar and honey from the diet. Lactosuria which is not uncommon in nursing mothers may appear in breast-fed infants with digestive disorders. Pentosuria arising apart from the ingestion of fruits, is a familial "inborn error" of metabolism and is not known to have any pathological significance.

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When true glycosuria has been detected it is of the greatest importance to determine its cause as soon as possible. Ketonuria as indicated by a positive Rothera Test is suggestive of diabetes mellitus but the association of ketosis with non-diabetic glycosurias is not uncommon. A single blood-sugar estimation is of value especially if the sample is taken in the post-absorptive state. If the blood-sugar of the fasting specimen is above 140 mg. per cent., or that of the sample taken in the course of the day some hours after a meal is above 200 mg. per cent., it is wise provisionally to presume the case to be one of true diabetes mellitus. If, however, the above figures are not reached it is necessary to estimate the course of the blood-sugar after the ingestion of glucose.

The Blood-Sugar Curve.

In children it is usual to determine this immediately before and after the ingestion of one gm. of glucose per kilo. body weight. The child should be in the post-absorptive state so that the test should be carried out in the morning before any food has been taken. Three points are to be noted in the curve (a) the fasting level, (b) the height of the peak, and (c) the time taken to reach the fasting level. Normally the fasting level should fall between 80 and 120 mg. per cent. depending on whether capillary or venous blood is used and on the method of analysis. As a general rule it may be said that the fasting blood-sugar is lowest in the early months of life, rises with advancing age until at three years it is on the same level as that of the adult. The peak of the curve, which depends on the rates of absorption and storage, is usually reached at 30 minutes and should not exceed 200 mg. per cent. Within 2 hours the blood-sugar should have returned to the fasting level.

Factors Affecting Blood-Sugar Curve.

(a) Dosage of glucose. In a child an increase in the amount of glucose ingested raises the height of the curve and causes a delay in the return to normal.

(b) Exercise before the ingestion of glucose frequently produces a slight increase in the fasting value while if there is any muscular exertion after the ingestion of glucose the peak is lowered and the fall quickened.

(c) Time of day. It has been shown that in over 60 per cent. of subjects the same dose of glucose gives a higher peak when given in the afternoon than in the morning.

(d) Nausea. If the ingestion of glucose leads to nausea, the rise of blood sugar is considerably lessened and possibly prevented owing probably to inhibition of peristalsis and diminished absorption.

(e) Emotional disturbances are specially liable in childhood to produce a rise in the blood-sugar curve.

Renal Threshold.

During a blood-sugar tolerance test the urine should be examined for glucose before and one and two hours after the ingestion of glucose. The occurrence of glycosuria depends on whether the concentration of blood-sugar rises beyond that point at which the kidney excretes sugar in significant amounts: this is known as the renal threshold. It varies in different individuals but is said to remain

constant in the healthy subject throughout life. In an investigation in children Dr. Gilchrist found the renal threshold to vary between 180 and 310 with an average of about 230 mg. per cent. Much higher values have, however, been recorded in the literature. It is of interest to note that Faber and Hansen have found a lower threshold with a falling than with a rising blood-sugar.

Classification of Glycosurias.

Glycosuria may be divided into three groups.

- I. With low renal threshold—renal glycosuria.
- II. With normal renal threshold—non-diabetic.
- III. With normal renal threshold—diabetic.

I.—Renal Glycosuria.

This may be defined as a condition in which glycosuria occurs in spite of the fact that the blood-sugar even after high carbohydrate intake remains within normal limits. Several authors have pointed out its tendency to occur in families. It is not often seen in childhood probably because there are no symptoms which lead to the examination of urine for sugar. Graham has divided renal glycosuria into two groups, (a) intermittent, cyclic or continuous glycosuria with a low sugar output associated with a normal or flattened blood-sugar curve showing a quick return to the fasting level, (b) transient or continuous glycosuria with a much larger sugar output and associated with a curve which may be higher than normal and may show some delay in returning to the fasting level.

Everyone is agreed that the first group can be considered quite up to standard so far as carbohydrate metabolism is concerned: prognosis is good and treatment is not necessary. In order to establish the diagnosis it is essential to carry out a blood-sugar tolerance test. The presence or absence of ketonuria is no criterion, since this has been reported as occurring in association with renal glycosuria.

As regards the second group opinion is divided. Graham considers that there is diminished carbohydrate tolerance and Joslin also holds this conservative view. Reports are, however, appearing in the literature which seem to indicate that this type is not one of true diabetes. Thus Faber reports Holst's detection of 27 cases of this type among 163 so-called diabetics: these 27 have been under observation for periods of 1 to 25 years without any other sign of true diabetes mellitus appearing although the majority quickly reverted to ordinary diet. Because of the serious results of missing true diabetes, it is probably wisest to adopt Joslin's view and treat the condition as one of diabetes mellitus until the course of events shows that the glycosuria is innocent.

II.—Non-Diabetic Glycosurias with Normal Renal Threshold.

Alimentary Glycosuria. This is a rather unsatisfactory term applied to the transient glycosuria occurring in some individuals after a meal containing a large amount of carbohydrate. It is due ultimately to the blood-sugar rising above the renal threshold. The height of the blood-sugar depends upon the rates of absorption, storage and consumption so that the appearance of glycosuria may result from very rapid absorption with delayed storage. It was at one time common to estimate sugar tolerance by determining the amount of sugar that could be ingested without the appearance of glycosuria. As a general rule it may be said that the child can take glucose up to the point of nausea without glycosuria.

There are, however, a few apparently healthy subjects who show transient glycosuria even with moderate doses of glucose. To these may be applied the diagnosis of alimentary glycosuria but this should always be confirmed by a blood-sugar tolerance test. In a series of 28 children investigated at the Royal Hospital for Sick Children with regard to their ability to deal with glucose, Dr. Gilchrist found that 4 showed glycosuria, one with one gram of glucose per kilo. body weight, one with four, one with five and one with six grams.

Emotional Glycosuria. It has long been known that emotional disturbances are likely to give rise to glycosuria. This is attributed to the increased secretion of epinephrine with a consequent rise in the rate of glycogen breakdown in the liver. In one of our cases the prospect of irradiation with ultra-violet light for the first time was sufficient to raise the fasting blood-sugar level from 98 mg. per cent. to 210 mg. per cent. In some children and adolescents the playing of a game of football is accompanied with sufficient emotional disturbance to produce a marked rise in blood-sugar with glycosuria. Edwards and his co-workers have demonstrated that a definite hyperglycæmia occurred about the middle of a game of football but only in those players showing emotional excitement.

Cerebral Glycosuria. Probably allied to the last group are those cases associated with intra-cranial disturbances in which hyperglycæmia and glycosuria originate from over-stimulation of the splanchnic sympathetic with rise in the output of epinephrine. Glycosuria of this nature is comparable to that produced by "Bernard's diabetic puncture". Cerebral hæmorrhage, sinus thrombosis, embolism, concussion, meningitis, cerebral tumour and increased intra-cranial pressure have all been found to be accompanied at times with glycosuria. Occasionally this has led to mistakes in diagnosis. A child may be admitted in coma and the routine examination of the urine reveal abundant glucose and acetone. This naturally leads to the suspicion of diabetic coma. In the absence of a history of thirst and polyuria it is advisable in such a case to obtain cerebro-spinal fluid by lumbar puncture when an increase of cells and a positive Pandey test will frequently demonstrate the true cause of the glycosuria, and in the case of cerebral tumour or injury signs of involvement of the central nervous system will be elicited. The estimation of the blood-sugar is of little value in the differential diagnosis since it will be high unless the cranial condition happens to have occurred in a patient with renal glycosuria. Hyperglycæmia and glycosuria have also been reported as a sequel of encephalitis.

Glycosuria and Hyperthyroidism. Glycosuria is frequently met with in conditions of hyperthyroidism due to disturbance of carbohydrate metabolism. Unfortunately there is no blood-sugar curve typical of this condition. In the few cases observed at the Royal Hospital for Sick Children, Glasgow, the peak of the curve was high and the return to fasting level delayed. John, however, has pointed out that apparently normal curves are sometimes found in severe cases of hyperthyroidism and concluded that the renal threshold may be lowered. The association of hyperthyroidism with true diabetes mellitus is a matter of some importance. At present it is the opinion of competent observers that the combination of true diabetes and hyperthyroidism is rare. In a series of 1,800 cases of Graves' disease at the Mayo Clinic, Fitz found only 9 with true diabetes. As a general rule it has been found that the hyperthyroidism preceded the onset of diabetes and that the incidence of the latter was greatest in cases of toxic adenoma. The possibility is therefore not excluded that prolonged severe hyperthyroidism may tend to induce diabetes mellitus.

Pituitary Glycosuria. Owing to the fact that the functions of the pituitary hormones have not been completely worked out, much confusion still exists as to the relationship between the pituitary and carbohydrate metabolism. There is undoubtedly an antagonism between the pituitary secretion and insulin whether directly or as a result of opposite actions on the liver. It would appear that in the earlier or hyperpituitary stages of acromegaly there is intolerance for carbohydrate which may be so marked as to produce continuous glycosuria with hyperglycæmia almost indistinguishable from diabetes. Ketosis and coma may be features of tumours of the pituitary region and Fleming has reported a case in which marked glycosuria and ketonuria with coma led to the diagnosis of diabetic coma but which ultimately turned out to be one of supra-pituitary adamantinoma. Generally the blood-sugar curve is high in acromegaly although both the fasting blood-sugar and the value at two hours may fall within normal limits. In Fröhlich's syndrome (hypopituitarism) the curve that has been generally obtained by Dr. Badenoch* in this hospital is one characterised by a delayed return to the fasting level and not accompanied by glycosuria. In the literature, however, a flattened curve indicating an increased tolerance for carbohydrate is not an uncommon finding. It is probable that most of the cases which have been investigated by Dr. Badenoch have been in the early stages of the disease. Pituitary hyperglycæmia and glycosuria appear to respond to insulin just as does true diabetes. It is stated, however, that glycosuria resulting from overaction of the pituitary frequently undergoes spontaneous cure in contrast to what occurs in diabetes mellitus. This is probably due to the temporary nature of the hyperpituitarism which may rapidly change into hypopituitarism.

Glycosuria Associated with Infections. Hyperglycæmia and glycosuria of all grades are known to occur in the course of infections. It is probable, too, that a latent diabetes mellitus may be increased in severity and thus brought to light. The degree of disturbance of carbohydrate metabolism appears to depend less on the severity than on the site of infection. Boils, carbuncles and other pyogenic infections of the skin are specially liable to produce glycosuria. The disturbance in carbohydrate metabolism is frequently characterised by marked ketonuria as well as hyperglycæmia and glycosuria and may prove very refractory and even simulate true diabetes. It is indeed not certain whether the condition should not be considered as one of transient diabetes. Certainly dietetic and insulin treatment appear to be strongly indicated both for the disturbance of carbohydrate metabolism and for the beneficial effects on the infection. In infants with gastroenteritis, especially when associated with marked dehydration, glycosuria is frequently found and in the treatment of this condition with parenteral administration of glucose it is advisable to add insulin. Glycosuria has also been reported in many other forms of bacterial and protozoal infection.

Acidosis. Patients with acidosis occasionally show glycosuria. In 9 subjects prolonged administration of ammonium chloride induced glycosuria in 2. The blood-sugar curve during the same period showed a somewhat higher peak than normal and a delayed return to the original fasting level which was within normal limits. When ketosis is produced by the ingestion of high fat diet the change in the blood-sugar curve is much more marked than that produced by ammonium chloride although the glycosuria is not more frequent. Gilchrist concludes that the hyperglycæmia found with ketosis is only in small part due to the ketosis but is chiefly the result of increased accumulation of fats in the liver and the consequent

*Personal communication.

impairment of its glycogenic function. In clinical acidosis without ketosis glycosuria is not frequent but in acidotic conditions associated with ketosis, such as starvation acidosis and cyclical vomiting, glycosuria is occasionally detected. This may lead to the suspicion of true diabetes but in the non-diabetic acidosis the glycosuria usually occurs during treatment with high carbohydrate intake and does not appear after the acidotic condition has been relieved.

Post-Anæsthetic Glycosuria. The glycosuria which sometimes occurs after general anæsthesia appears to have some relation to the duration of the anæsthesia. It is associated with hyperglycæmia and is probably due to an increased rate of glycogenolysis. Frequently glycosuria is associated with ketonuria and actual coma may supervene. The absence of any previous symptoms and the fact that only a short time has elapsed since the administration of an anæsthetic renders its differentiation from true diabetes an easy matter. Although the general condition is one of the utmost gravity, the glycosuria *per se* is not of any serious significance. Insulin may be given chiefly to facilitate the combustion of carbohydrate but it is doubtful whether it is of any value. It certainly should always be accompanied with abundant glucose.

III.—Diabetic Glycosuria.

The diagnosis of true diabetic glycosuria is generally not difficult in childhood since in the majority of cases it is heralded by the onset of thirst and polyuria. In the absence of symptoms other than glycosuria it is advisable to perform a blood-sugar tolerance test. Hale-White and Payne have pointed out that only one type of blood-sugar curve is pathognomonic of true diabetic mellitus, viz.:—one in which the fasting level and peak are both high and the fall very prolonged. Diabetes mellitus may, nevertheless, be present with many other types of curve but conversely other forms of abnormal curve do not necessarily indicate diabetes. Frequently it is possible by a consideration of the joint clinical and laboratory findings—and incidentally laboratory findings must never be used without taking into account the clinical picture—to conclude that a case is not one of true diabetes mellitus. If, however, this is impossible it is wise to look on the condition as a true diabetic one until the future events declare whether or not the suspicion is well-grounded.

In view of the proneness of untreated juvenile diabetes to run a very rapid downhill course it is advisable to commence active treatment with as little delay as possible. Diabetic therapy in childhood is in essence no different from that in adult life. It depends for its success firstly on the administration of sufficient insulin to allow the carbohydrate metabolism to be carried on normally and thus to permit a reasonable diet being taken and secondly on careful and continuous after-care. It seems unnecessary at the present state of knowledge to insist on the fact that there is no virtue in reducing the insulin dosage at the expense of glycosuria and dietary restriction. But experience with parents and doctors has shown one that there is a strong tendency to keep the insulin dosage low even when the patient is excreting abundant glucose in the urine. The result almost invariably follows that it is much more difficult to restore carbohydrate metabolism to normal and occasionally disaster ensues before the necessary steps can be taken. After-care, of advantage for patients of all ages and with all types of disease, is of vital importance for diabetic children. The child presents special problems of his own, such as growth and the increased liability to infection both of which throw an extra strain on the metabolic processes.

As soon as the diagnosis of diabetes is made it is essential to initiate treatment and this can be done in one of two ways. In the first the diet is reduced until glycosuria has disappeared and thereafter it is gradually increased up to the required intake the glycosuria being controlled by the administration of insulin as and when required. In the second method the optimum requirement of diet is given at once and sufficient insulin administered to prevent glycosuria. The amount of insulin required can be gauged approximately by estimating the amount of glucose excreted per 24 hours in the urine, and allowing one unit of insulin for every two grams of urinary sugar. In the choice of methods it is to be remembered that children are much more liable to acidotic conditions than are adults. Accordingly, if acetonuria is marked, it is advisable not to restrict carbohydrate unduly but to give a fairly liberal supply along with insulin since sudden restriction may increase the ketosis and precipitate coma. If, however, the Rothera's test gives but a mildly positive result, the first or crescendo method is probably the one of choice since it enables one to determine the carbohydrate tolerance before insulin administration is commenced. Furthermore, less strain is thrown on the organs concerned with carbohydrate metabolism and glycogen storage in the liver is a more gradual process. With gradual increase in the insulin dosage there is less likelihood of hypoglycæmia occurring with consequent undermining of the patients' and parents' confidence before that has been fully established. Lastly, there is a tendency to overfeeding when too little attention is paid to diet and too much stress is laid on insulin therapy. Although the gradual increase of diet to the required amount is recommended, it is wise not to spend too long a time in adjusting a fine balance between the insulin requirements and a diet of low caloric value. The patient becomes wearied and is liable to develop the invalid outlook whereas it is important that he should realise that apart from requiring insulin and dietary regulation he should, and with care will, live an ordinary life with no other restrictions.

Dietary requirements must satisfy the caloric needs of the child. It is generally accepted that the diabetic patient is better when below average weight and since the overweight child is specially liable to show abnormalities of fat metabolism and to coma we have found that children get along better when the caloric value of the food supplied is less than that generally recommended for healthy children of the same age. Overactive children will naturally require more than lethargic: in Joslin's clinic the caloric intake is increased by ten per cent. for very active patients. Insistence on too low a dietary defeats itself by leading to illicit breaking of the dietary regimen. There is no reason why the child should not satisfy his appetite provided the amount of food taken is weighed. The safe rule is to ensure that the child gets sufficient but no more than sufficient to allow of normal development. For this reason diabetic children should be weighed at regular intervals and the diet adjusted accordingly. In actual practice we have found that a caloric intake exceeding the basal requirements by 50 per cent. is a very useful standard and that only rarely does the child's appetite or state of nutrition demand more. As regards the partition of the diet among the various proximate principles, opinion has now veered to a more liberal supply of carbohydrate as far as the adult patient is concerned. Apparently with a large carbohydrate intake the insulin required increases little if at all. In the child, however, we feel that on the whole it is wiser to restrict the supply of carbohydrate to a quarter of the total caloric intake. This is because of the greater liability of the child to infection and consequent reduction of the potency of insulin. Probably the best guiding principle is to arrange the diet so that, though adequate, the minimum amount of insulin

is required to keep the urine free of sugar and acetone. It is still an open question, however, whether the restriction of the food value of carbohydrate to 25 per cent. of the total calories is the best way to achieve this desideratum. As regards fat there is no doubt that the intake should not in the child represent more than 60 per cent. of the total calories, since a high fat diet is not tolerated well by the child or adolescent. The quota of protein will depend on the age and weight of the child, but 20 per cent. of the total caloric requirements should in all cases suffice.

In actual practice we have found that a modification of the Lawrence line diet provides a very suitable scheme for regulating the diet. The red line has been modified so that each contains 7.5 gm. of protein plus 7.5 gram. of fat with a caloric value of 100: the black line corresponds to 5 gm. carbohydrate with a caloric value of 20. In prescribing a diet it is easiest first to allot sufficient black lines to make up 25 per cent. of the total calories: this is easily done by dividing the carbohydrate calories (one quarter of the total) by 20. The number of red lines are obtained by dividing the non-carbohydrate calories (three quarters of the total) by 100. An example will make this clear.

A child aged 8 years requires approximately 1,200 calories.

Carbohydrate Calories	...	...	=	300	
Number of black lines	...	...	=	$\frac{300}{20}$	= 15
Non-carbohydrate Calories	...		=	900	
Number of red lines	...	...	=	$\frac{900}{100}$	= 9

This ensures a sufficiency of protein. It may be desired to give less carbohydrate and the diet may be arranged accordingly but it is necessary that for every red line there is at least one black line.

Two important requirements must be borne in mind when instituting any scheme of treatment. It must be easily understood and managed. Furthermore, it must be possible to vary the diet readily and so prevent monotony. The line dietary satisfies these requirements: since its adoption some years ago in the diabetic clinic of the Royal Hospital for Sick Children, Glasgow, it has proved a boon to the mothers of the patients, since they can understand it and are better able to cope with the desires of the children.

There next falls to be considered the distribution of the diet throughout the day: this is clearly bound up with the administration of insulin. The ideal method would be to distribute food and insulin equally throughout the 24 hours but this is inconvenient for domestic reasons and also because it necessitates too many injections. Probably the best method is to give two large meals at breakfast and supper and thus limit the injections of insulin to two. A single injection of insulin may suffice in the very mild cases and in this circumstance it should be given before the largest meal of the day. Occasionally when the insulin effect wears off quickly it may be necessary to give three injections. The actual spacing of diet and insulin should be so arranged that there is no glycosuria. This can be most readily accomplished by testing the urine before each meal. Thus the time of sugar-leakage is detected, and to prevent this, appropriate changes in diet and insulin can be made.

For the satisfactory carrying out of the treatment it is necessary to instruct the child (or if too young, the mother) in the use of a syringe and the testing of urine. For the latter purpose Benedict's qualitative reagent is used. Six drops of urine are added to half an inch depth of reagent in a test tube which is immersed in a pan of boiling water for 5 minutes when the presence or absence of reduction is noted. It is advisable that records of the results of urine tests should be kept. Both patient and parents should be impressed with the necessity of keeping the urine sugar-free. If glycosuria is present it is exceedingly difficult to determine the state of the patient without frequent blood analysis. When parents realise this their supervision becomes more careful and the obtaining of negative tests encourages both patients and parents. If, however, occasional glycosuria is treated too lightly, carelessness is engendered and gradual worsening of the condition ensues which often terminates in coma. As a general rule the aglycosuric state is attained, but occasionally it seems impracticable to achieve this without producing severe hypoglycæmic attacks. Such cases are fortunately not common and are probably due to an abnormally low renal threshold. Indeed, there have been published the records of some patients with true diabetes mellitus associated with renal glycosuria. The opposite condition of high renal threshold is more frequently encountered: this will mask any deterioration in the sugar tolerance so that it is advisable, even in the absence of glycosuria, occasionally, perhaps once a year, to estimate the blood-sugar. The presence of a septic focus lowers the tolerance for sugar and necessitates an extra supply of insulin. Catarrhs of the upper respiratory passages also have a deleterious effect. Now that insulin has rendered surgical procedures safe in diabetes it is advisable to remove any offending cause, such as enlarged tonsils or adenoids. Glycosuria is much more common during the winter months: this is almost certainly due to the greater prevalence of catarrhal infections. In all these circumstances the insulin dosage must be temporarily increased so as to prevent glycosuria, if possible. The former state of carbohydrate tolerance is generally regained as soon as the acute stage of the infection has passed, so that it is necessary to be on guard and reduce the insulin as the infection subsides since otherwise a hypoglycæmic reaction may occur.

The only risk of insulin therapy is the liability to attacks of hypoglycæmia. It may be stated at once that hypoglycæmia, if promptly treated, is not a dangerous condition. The fear of hypoglycæmia should not lead to under-administration of insulin. The risk is much greater when too little insulin is given than when too much. The maximum effect of insulin is usually observed about four hours after the injection but occasionally a hypoglycæmic turn may occur as soon as half an hour after the insulin has been given. Muscular exercise by its call on the carbohydrate stores of the body leads to a reduction in blood-sugar which may fall below the critical level. This is more likely to occur in the child than the adult whose glycogen stores are very much greater. In one patient hypoglycæmic attacks occurred regularly on Friday evenings during the summer months: these remained inexplicable until it was discovered that he indulged in football only on this evening of the week. The increase in muscular exercise on leaving hospital probably explains the occurrence of hypoglycæmic turns after the patient returns to his home. Since only very severe diabetics fail to react to exercise by reduction of blood-sugar it is wise to allow for this in the event of any unusual exercise being performed. Another occasional cause of hypoglycæmia is gastro-intestinal disturbance with interference with intestinal absorption: in these circumstances insulin shock is prone to occur.

The premonitory symptoms and signs of hypoglycæmia are readily recognised by the parents and in some cases by the children themselves after one attack. Usually the first symptom of impending hypoglycæmia is a tingling feeling in the fingers. This is quickly followed and sometimes preceded by a sensation of hunger and profuse sweating. If steps are not taken to combat the hypoglycæmia the patient becomes delirious and a convulsion may ensue. In some children the attack may resemble a fit of hysteria. The onset is most difficult to detect in very young patients but undue quietness of the child associated with pallor and perspiration ought to raise the suspicion of hypoglycæmia.

Priscilla White in a recent monograph on Diabetes in Childhood emphasizes the importance of differential diagnosis of hypoglycæmia and coma. She summarises the most important clinical differences as follows. The loss of consciousness is rapid in insulin shock, gradual in coma. The cause of hypoglycæmia is overdosage of insulin, reduction of diet or increase in exercise, while that of coma is omission of insulin, lapse of dietary control or infection. The skin in insulin shock is moist and pale but dry and flushed in coma except in the late stages. The breathing is normal or shallow in shock but deep and rapid in coma. In shock the pulse is full and bounding, in coma weak and rapid. While vomiting commonly precedes the onset of unconsciousness in coma, it is exceptional in shock and when it does occur generally follows unconsciousness. A hypoglycæmic attack if at all marked is usually attended by a convulsion, while in coma convulsions are absent unless alkali therapy has been used. Blood analysis will, of course, establish the diagnosis since in coma the blood-sugar is high and the alkali reserve very low, while in shock the blood-sugar is low and the alkali reserve normal or rather high. In the absence of laboratory facilities urinary tests for glucose and acetone are of value but it must be remembered that the urine may have been secreted before the fall of the blood-sugar and therefore may contain glucose. A second specimen in insulin shock will be sugar-free whereas in coma glycosuria will still be marked.

The treatment of hypoglycæmia is simple. A small amount of sugar in the form of lump-sugar or sweetened orange juice given at the onset of a turn usually causes rapid recovery. If the symptoms are more severe before treatment has been instituted, an injection of adrenalin (about five minims) will produce a return to complete consciousness within a few minutes.

The one complication to be feared in diabetes in childhood is coma. In contradistinction to the experience in adults, in whom pulmonary phthisis and severe skin infections are the chief causes of anxiety, in children death is almost invariably the result of coma that has been unsuccessfully treated. In pre-insulin days Joslin described the position of children as living in a state of coma deferred. The onset of coma is due to continued insufficiency of insulin generally brought about by breaking of the dietary régime but which may easily be induced by an infection in a patient whose insulin and diet had previously been satisfactory. Occasionally the presence of the diabetic condition is first detected when the patient is in coma but this is generally due to the symptoms of thirst and polyuria being ignored, since it is very rare for coma to be the first manifestation of diabetes. Furthermore, an attack of diabetic coma is generally heralded by certain premonitory symptoms. The occurrence of headache, general malaise, nausea, vomiting, abdominal pain and constipation in a patient with diabetes is almost invariably the forerunner of coma. The abdominal pain may be so severe as to lead to the suspicion of an acute abdominal crisis and it is not a rarity for the surgeon to be called in. It may be wise to mention that quite a marked leukocytosis is frequently associated with coma even in the absence of a severe infection so that a blood-count is of

little value in the differential diagnosis. The finding of glycosuria and acetonuria usually points to the true cause of the condition. Cases are on record in which acetone has been absent from the urine. Two other findings are not uncommonly present, viz.:—the presence of albuminuria and the occurrence of casts in the urine. As regards the other clinical phenomena little need be said. The respirations are laboured and increased in frequency, the pulse frequent and feeble, the blood pressure low and the temperature generally subnormal. The tension of the eyeball is said to be invariably low. The reflexes are normal but an extensor type of plantar response has been reported, thus minimising the importance of this finding as an index of hypoglycæmic coma.

The treatment of coma is based on a rational understanding of the disturbed physiology. This may be summarised under the following headings: (1) insufficient oxidation of glucose, (2) presence of acidosis due to accumulation of ketones, (3) loss of water (dehydration) and salts especially sodium chloride. The last of these is of considerable importance because the unsuccessful treatment of coma is not infrequently due to neglect of this factor. The general lines of therapy are therefore administration of insulin and carbohydrate and the plentiful supply of fluid with salt. It must be emphasized that diabetic coma is an emergency of as great urgency as an acute abdominal condition and must be treated actively without delay.

The first aim is to abolish the acidosis. This can be done by ensuring the effective oxidation of glucose for by this means the formation of ketones is prevented and the oxidation of those already present is accelerated. To achieve this, large doses of insulin are injected at frequent intervals: simultaneously large quantities of glucose are given *per os*, *per rectum*, subcutaneously or intravenously. The administration of glucose is advisable in all cases (and especially so when laboratory facilities for blood analysis are not available) since in many the store of carbohydrate is very depleted. When glucose is given with insulin the risk of converting coma to hypoglycæmia is negligible. The urine should be examined frequently for glucose and acetone, but the clinical condition of the patient affords the best guide as to the necessity for increasing or decreasing the dosage of insulin and glucose. The amounts to be given naturally vary with the age and weight of the patient and the severity of the diabetes and coma.

The second aim, which is as important as the first, is to replenish the depleted stores of water and salt. This may be best accomplished by supplying the glucose in the form of a dextro-saline solution (10% glucose in normal saline). Should it be desired for any reason to diminish the intake of glucose it is imperative to continue with the administration of saline which can be given either by the mouth, rectum, or parenterally. In cases where the acidosis is marked and recovery slow, alkali as sodium bicarbonate may be given orally, but vigorous insulin-glucose-saline therapy is usually sufficient. The other important points in the treatment are application of warmth, induction of free action of the bowels and, if necessary, gastric lavage with an alkaline solution to decrease vomiting.

Diabetic coma has now almost reached the status of an avoidable accident. The parents of diabetic children must therefore be educated as to the significance of the various danger signals and the special liability of the occurrence of coma in the presence of an infection. They should also be given definite instructions regarding the immediate treatment when symptoms suggestive of impending coma

become manifest: the doctor should be immediately sent for and meanwhile the child should be kept warm in bed and be given hot drinks, containing carbohydrate, if possible with saline, and an increased dose of insulin.

The discovery of insulin has entirely changed the prognosis of diabetes in childhood. Whereas in pre-insulin days the outlook was almost hopeless, the patient seldom lived longer than two years, the prognosis now appears to be very favourable. Growth is perfectly normal as are physical and mental activity, and there does not appear to be any increased susceptibility to infections although the onset of an infective process makes the treatment temporarily more difficult and anxious. Growth and mental development proceed quite normally. Some of Joslin's diabetic patients have become mothers and all lead perfectly normal lives apart from the necessity of diet regulation and insulin administration. The secret seems to be the education of parents, and of the children when old enough, in the principles and details of treatment. In addition, the importance of supervision by the family doctor or in a properly constituted diabetic clinic cannot be over-emphasized since this goes far to prevent the occurrence of the serious complications and ensures the correct adjustment of insulin dosage and diet to the increasing needs of the growing child.

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THE HIPPOCRATIC TRADITION.

By MATTHEW B. RAY, D.S.O., M.D.(Edin.)

The Hippocratic Writings.—continued.

4.—Epidemics.

This book was probably a note-book and not intended for publication in its present form. The few extracts given below are excellent examples of concise note-taking because not a word is wasted and the descriptions are always to the point. It is divided into a description of certain "constitutions" or climatic conditions of a marked type which distinguish a definite period of time. The word also applies to a fixed type of disease prevalent at any particular period, while the general accounts of the epidemics seem to bear some relationship to the weather conditions that precede them, the case histories have apparently nothing whatever to do with the "constitutions". As an example, the first part of the first "constitution" is given:—