5-1-1935

Juvenile diabetes

Paul J. Huber
University of Nebraska Medical Center

Senior Thesis

JUVENILE DIABETES

Paul J. Huber

1 9 3 5

JUVENILE DIABETES

TABLE OF CONTENTS

JUVENILE DIABETES

INTRODUCTION

Diabetes mellitus is a disease of particular interest, since it is a departure from the physiologic condition involving the capacity of the organism to care for sugar in the normal fashion.

The diabetes of juveniles differs in many respects from that of adults. Juveniles represent only 5 per cent of the total number of all diabetic patients.

The diabetic child at onset of his disease is usually taller and heavier than the average child and is mentally precocious. The management of the diabetic child has always been a source of great worry to physician and parent. Joslin believes that the most important education for a diabetic child is his diabetic education, because upon that his life depends. (25)

In order to command the greatest co-operation the lives of diabetic children should resemble as nearly as possible the lives of other children. The choice of diets in feeding diabetic children are those which are as nearly similar to the diets fed normal children as possible. They are high in carbohydrates and low in fats. (4) The necessary reduction of carbohydrate in the form of sugar, bread, cereals, and fruits other than those of the citrus family, together with the withdrawal of milk from the diet, is a more serious deprivation than in the case of the adult. (21)

The importance of diabetes mellitus in children lies not so much in its frequency of occurrence, for it is a relatively rare disease, as in its severity. When the older literature prior to the discovery of insulin is studied, one is impressed with the hopeless outlook in juvenile diabetes. (39) Fowler in 1891 said "no recoveries from diabetes mellitus occurring in children have been reported. In fact, the disease is very fatal." Osler in 1917 stated that he personally had not known of a case of recovery in a child. Holt in 1917 stated that in few diseases has the prognosis been so bad as in diabetes in children, but that the outlook was not so immediately dark as it had been because of the recent methods of treatment; and Joslin and White in 1928 gave a mortality rate of 1 per cent per year for 303 patients over a period of twenty-two months.

The physician who treats diabetic children today aims to have them reach adult life with as good physical development as possible. Fischer states that they should be able to carry on their daily life like normal children of their own age. (14)

There are certain cases of severe diabetes which are extremely difficult to control, cases which require large doses of insulin three or four times a day and in which the patients pass rapidly into a state of acidosis if an injection is missed or if the dosage is inadequate. Before the discovery of insulin careful treatment frequently controlled juvenile diabetes and prolonged life for a considerable time, but the ultimate fate was rarely avoided.

With increasing age the diabetic child who has demonstrated his ability to carry on the normal functions of childhood and youth faces a new problem in the possible transmission of his disease. White believes that the hereditary taint in the diabetic child is evident. (49)

The decreasing severity of diabetes, the absence of its complications in the child treated with insulin from the very onset, and the actual lack of organic disease of the pancreas offer limitless hope for the future of the diabetic child.

ETIOLOGY

It is possible that the high carbohydrate diet in the latter part of the first year of life is a contributing factor to the high incidence of appearance of symptoms of diabetes mellitus in the second year of life. The incidence of the disease is highest in northern Europeans, especially those of Scandinavian extraction. This may be explained in part by the observation that the usual Scandinavian diet contains a high proportion of carbohydrates. (39)

The first inkling that the pancreas is necessary for the complete utilization of carbohydrates in the animal body dates as far back as 1682. In this year Brunner published a work entitled "Experimenta Nova Circa Pancreas" in which he describes the general behavior of dogs after removal of all of the pancreas save the portion which we now call the tail or splenic end. (32)

Cammidge suggests that diabetes mellitus may develop from inherited defects in the pancreas, recessive in nature, "which prevent the development of the organism in a particular direction from keeping pace with the increasing demands of the growing body, and as the inherited factor probably differs in intensity, so the period of life at which the symptoms of diabetes appear also varies." (8)

The evidence of the inheritance of diabetes rests primarily on three facts; first, the occurrence of diabetes in homologous twins; second, the greater incidence of diabetes in the relatives of a diabetic person than in a control population; and third, indirectly, on the demonstration that mendelian ratios are found in large series of case histories selected at random and in smaller series of families tested for accuracy of diagnosis and for latency of the disease. White, Joslin, and Pincus believe that the potentiality for developing diabetes is transmitted as a simple mendelian recessive trait and that the secondary factors which permit the expression of the gene can best be studied among predestined diabetic patients; namely, homologous twins of diabetic patients and the offspring of two diabetic patients. (50)

Of 26 sets of twins (13 sets similar) each member of similar twins developed diabetes more than four times as frequently as each member of dissimilar twins.

The incidence of diabetes in the relatives of a diabetic population is significantly greater than in a nondiabetic group. Many blood relatives of diabetic patients have symptomless hyperglycemia the significance of which is unknown.

In Mackler and Fischer's series of fifty-seven juvenile diabetic patients, some of whom have been observed for as long as nine years, no brother, sister or parent developed diabetes during that time. (31) Since the onset of diabetes in children and in adolescents, is as a rule, rather sudden, it is felt that the sugar tolerance method does not hold much promise as a means for detecting early cases of diabetes in childhood. Thirty siblings of juvenile diabetic patients were examined. Their sugar tolerance curves were within normal limits. Of these, twenty-one were reexamined six years later. In none of this group had diabetes developed. Five siblings whose curves suggested a decreased tolerance for carbohydrate in 1928 were retested in 1934. The curves gave normal values and showed no prediabetic tendency.

At present it is not clear whether the inherited factor is itself the determining cause of diabetes although there can be no doubt that heredity plays a part in the production of the defects of carbohydrate metabolism, giving rise to glycosuria and diabetes in many instances. Cammidge (8) believes that there is not as yet sufficient evidence to justify the conclusion that an inherited factor is a necessary basis for the development of these conditions in all cases.

It is well known that the occurrence of a complication, especially a febrile illness, brings about aggravation of diabetes. Sometimes mild diabetes becomes extremely severe, and the difficulty in controlling the disease is a source of danger. (1) In 1918 and 1919 many of the new cases of diabetes appeared during or after influenza. (51)

Overgrowth is an almost constant characteristic of the prediabetic child. (49) It has been reported in over 90 per cent of Joslin and White's children measured within three months of onset, in 88 per cent of Ladd's diabetic children, and in the majority of the children studied at the Children's Hospital, Boston, and in the seventy-one children studied by Rabinowitch. The significance of overgrowth is puzzling.

Of thirty-four cases studied by Ladd all but four occurred in patients who were either overweight or overgrown, or both, at the onset of the diabetes. (29) He believes that there is no other etiologic factor as significant. In two of his remaining cases, onset of diabetes occurred after acute infection. In one, no etiologic factor could be suggested.

Overheight in the child, Joslin and White believe, corresponds to obesity in the adult. (49) Just as obesity need not reach extremes before the onset of diabetes in the adult, overheight need not reach extremes before onset of diabetes in the child. Overheight may be the result of optimum nutrition or infections with their subsequent gains in length. Overgrowth may be associated with hyperactivity of the other glands of internal secretion, particularly the pituitary. Since the etiology of diabetes in the child is still a mystery the possible combination of an hereditary taint and an environment producing maximum growth must be considered.

Diabetes in the Jew tends to be inherited as a dominant characteristic and less frequently develops in the very young child. (39)

MORBID ANATOMY

Langerhans, an anatomist, in about 1869 properly described the peculiar collections of cells in the pancreas, now known as the Isles of Langerhans. Sir E. Sharpey Schafer definitely suggested in 1895 that pathological changes in the islets might be responsible for diabetes. (32)

Warren (47) made a study and recorded pathologic conditions found in ten cases of diabetes occurring in children from 2.2 to 14.7 years of age at the time of onset of diabetes mellitus. The duration in one instance was twenty-nine years; in the others, from seventeen days to five and one-half years. All but one of these patients died in coma, and that one was killed in an automobile accident. Startling pathologic change was not evident. The pancreas was noted as small in most cases. The size of the pancreas varies considerably even in normal persons. His conclusion was that apparent pathologic changes of the pancreas are not present in most cases of diabetes in children.

In a study of one hundred and forty-seven autopsies by Gibb and Logan on diabetics interstitial pancreatitis was present in one hundred and twenty-three cases. (16) 64.8 per cent of these showed interacinar, and 19 per cent, interlobular, fibrosis. 53.7 per cent of the cases showed a well developed interstitial pancreatitis. This lesion showed a definite increase with age. Only 8 per cent of cases in individuals from ten to twenty years of age showed interstitial pancreatitis. In this group there were no cases of lipomatosis and only 8 per cent showed arteriosclerosis.

Warren states that lymphocytic infiltration of the islands, found among children, is a lesion not encountered in older diabetic patients, and that hyalinization of the islands is not found in the young. (47) He believes that there is little pathologic change in either islands or acinous tissue, though commonly reported in the old, and that that present does not appear sufficient to account for the marked disturbance in function.

Robertson (44) states that the pancreatic lesions might be expected to become worse until life is no longer possible but that diabetic children can be kept healthy with insulin even if the disease is of long standing. It is his impression that the severe cases may have no power of secreting insulin or so little as to be clinically negligible but there must be some factor preventing the pancreas from degenerating further. During the last few years children with diabetes have tended to require progressively more insulin until they require one unit for each 1.5 grams of potential carbohydrate in the diet. It is suggested that at this stage they are not secreting an appreciable amount of insulin, because (a) experiments show that one unit corresponds to about 1.5 grams of glucose; and (b) exhaustion of the pancreas is the simplest explanation of the disease ceasing to be progressive at this stage.

The absence of demonstrable injury indicates that diabetes mellitus in children is not ordinarily due to destruction of island tissue. The hope that function may be restored under favorable circumstances is not beyond possibility. In children, through treatment which allows the element of time to act, irreversible changes in the pancreas may be avoided. (47)

PHYSIOLOGY

Diabetes mellitus and hyperinsulinism presumably represent opposite secretory states of the pancreatic islets; the former, hypoactivity, and the latter, hyperactivity. Harris (18) states that it seems probable there are other dysfunctions of the islands of Langerhans, besides hypoinsulinism, and that an excessive formation of insulin may occur. Hyperinsulinism should, he believes, produce definite results such as a reduction in blood sugar, which when below a certain limit, about 0.070, brings on characteristic symptoms, now known as the insulin reaction. It also seems probable that a deficiency of the secretion of insulin may follow prolonged excessive work of the islands of Langerhans; just as in other glands, or organs hypertrophy and hyperactivity may be followed by degeneration, atrophy and loss of function.

Carbohydrate is the greatest energy producer. A certain amount of carbohydrate is also essential for the proper combustion of fat and protein and to neutralize the ketonic acid end-products of the combustion of fat.

The carbohydrate of the usual mixed diet consists of about equal parts of starch and sugar and the best digestive conditions seem to exist when these proportions are maintained. The infant takes most of the carbohydrate as sugar, mainly lactose.

The fate of sugar in the body may be divided into four steps; first, the absorption from the intestinal tract; second, the passage through the blood and occasionally elimination in the urine; third, the penetration into the tissues; and fourth, the disposal in the tissues. The rate of absorption is independent of the sugar concentration present in the intestine. (12)

The glucose supply is derived from carbohydrate, protein, and fat. 100 per cent of utilizable carbohydrate is convertible into glucose. Protein yields by digestion or in the course of catabolism amino acids of which some are convertible into glucose. (3) Fats on saponification yield glycerol which is convertible into glucose. A mixture of fats contains about 10 per cent glycerol.

The actual minimum protein requirement in children is that amount of protein which will establish a positive nitrogen balance, prove adequate for growth in stature, promote normal development, and allow the child to gain in weight at a normal rate. (6) The protein consumption of normal children has been estimated to vary from 2 to 4 grams of protein per kilogram of body weight; 2 grams in adolescence and 4 grams in infancy and childhood. Nitrogen equilibrium has been established in a boy aged 13, at rest in bed, receiving 1.25 grams of protein per kilogram of body weight.

Bartlett states that children require more protein per kilogram than adults because they must grow and develop.

A diet containing half its calories in carbohydrates and half in fat has the same protein protecting power as one made up of carbohydrates alone. This demonstrates the rationality of a mixture of the non-nitrogenous food-stuffs.

The variations of blood sugar in the child are excessive. (48) In the fasting state the blood sugar may be three or four times the normal value, and yet three hours after the child has received insulin and has eaten breakfast the blood may be at hypoglycemic levels.

Experimental evidence has proved that the blood sugar contains fermentable sugar other than glucose. (15) This unknown fermentable sugar is not maltose or any other di- or poly-saccharide. The unknown sugar is presumably produced within the organism and represents some phase of the intermediary metabolism of carbohydrates.

McLean and Sullivan found that children with diabetes mellitus gave high, prolonged blood sugar curves. (35)

BLOOD SUGAR CURVES FOLLOWING INGESTION OF DEXTROSE

Sex	Age	Body Weight Gm.	Control	Blood Sugar Mg. per 100 CC After ingestion of dextrose 1 hr.	2 hr.
M	3 yr.	14,400	258	302	374
F	4 "	12,900	214	441	420
M	4 yr. 10 mo.	14,375	63	309	286
		Normal Infants			
F	2 yr.	10,570	90	104	127
M	2 "	11,600	97	124	103
F	30 mo.	11,970	103	136	129

When the affinity of the cell for carbohydrate is rendered inactive, as in diabetes, fat alone is oxidized for the maintenance of the body.

Rabinowitch (43) studied forty-six children in an attempt to determine statistically whether in juvenile diabetes plasma cholesterol is related to, and can afford an index of, progress. A comparison was made between plasma cholesterol of diabetic and nondiabetic children at the Shriner's Hospital for Crippled Children, Montreal. The cholesterol, per cent is as follows:

Subjects	No. of cases	Maximum	Minimum	Average
Nondiabetic	44	0.234	0.111	0.176
Diabetic	46	0.600	0.120	0.243

All subjects were divided into two groups; (a) twenty--those who had glycosuria, and (b) twenty-six--those whose urines were sugar free.

Subjects		Average Cholesterol per cent
(a) Glycosuria	20	0.285
(b) No glycosuria	26	0.184

The difference between the average amount of cholesterol of the two groups is the result of the degree of control of the diabetes.

The relationship between cholesterol content of blood plasma and insulin dosage was determined as children in whom the diabetes is not controlled, tend to have a high cholesterol content in the blood.

Group	No. of cases	Average Cholesterol per cent
Able to decrease insulin dosage	20	0.200
Unable to decrease insulin dosage	26	0.277

It is certain that insulin dosage is related to the plasma cholesterol and appears that the plasma cholesterol of juvenile diabetic patients affords the same index of progress for the child as it does for adults.

SYMPTOMS

All the symptoms in diabetes are due to the departure from the physiologic condition involving the capacity of the organism to care for sugar in the normal fashion. Before the appearance of glycosuria it is difficult to prove that diabetes exists.

MacLeod calls attention to a description of interesting observations of Brunner in 1682 as quoted from the translation given in Sir Michael Foster's "History of Physiology," that "it was especially to be seen that an animal with the spleen and later the pancreas removed made water very frequently and that he was very thirsty, drinking largely of water in proportion to the discharge of urine." (32) Brunner, therefore, discovered that the removal of the pancreas produces the cardinal symptoms of diabetes. MacLeod also mentions another experiment in which the pancreas alone was removed by Brunner. After the operation this animal was very hungry. It was continually going to its former home and stealing food.

Since excessive hunger is a symptom of hypoglycemia, it may be that normal hunger is the call for glucose and that it may be in part or wholly of pancreatic origin and not entirely an expression of an empty stomach. (18)

Growth in height in children with diabetes mellitus diminishes or stops completely depending upon the severity of the case, and appears to be due to lack of food. (29) The impulse for growth in height seems to persist longer under the adverse conditions of diabetes and to be slower in starting again than the impulse for changes in weight.

Underweight to the extent of 11 pounds (5 kg.) or more was present in 15 per cent of 256 children of Joslin's series. (28) Only 2 per cent were more than 20 pounds (9 kg.) underweight and one of these has been in the hospital for a year. Although there were 33 per cent of the patients at least 5 pounds (2 kg.) below standard.Joslin states that today it is the exceptional diabetic child who is underweight or underheight, and when these lowered states of nutrition are encountered they should be combated as vigorously as in the nondiabetic child.

Although after years of the disease there is some evidence that physical growth may be retarded, the stature of the child does not fall appreciably below the standard average and mental growth continues above the normal average. (49)

As a class diabetic children do remarkably well in school and a number of them keep on the honor roll. (7) Beck applied the Binet-Simon test (Stanford revision) to seven diabetic patients. He found that their mental age was considerably above their chronological age, varying from one to three years.

White (49) states that the mental age of the diabetic child is eight months in advance of his chronological age.

It appears that the adult diabetic patient who is treated with insulin compares quite favorably with the normal individual with the exception that the majority have the subjective impression that they are not capable of normal physical effort without fatigue. According to Bowen (7) children apparently do not show this physical limitation.

TREATMENT

The treatment of diabetes mellitus in the juvenile patient is most satisfactory when the patient has acquired the fundamentals of his disease and how to combat it successfully. Joslin (25) states that the child must continually adjust the diabetic load between Diet, Exercise, and Insulin, and that he should not be discouraged despite frequent failures, because it can be done. The general health of diabetic children should be kept at its highest pitch.

Before the discovery of insulin and for a period afterward, many authors stressed the importance of keeping diabetic children entirely sugar free. In the early stages of the disease the fasting blood sugar of the juvenile patient drops to normal values very promptly following the institution of treatment. White (48) states that the response is more rapid than the corresponding response of the average adult.

Fischer (14) believes that while one still attempts to keep juvenile diabetics sugar free, it is possible in so doing to defeat the primary purpose, the production of normal growth and development.

In the management of diabetes in children early recognition and adequate treatment are the most important factors for obtaining good results. (7) A routine of controlled diet and insulin is essential and the prognosis depends almost entirely on its efficiency. (43)

The starvation method of treatment in the Allen era, about 1915 was an advance in the dietary management. This method was supposed to give the diseased pancreatic function opportunity to recuperate by more or less complete rest. When the glycosuria disappeared the total caloric intake, as well as the carbohydrate intake, was kept at a level low enough to maintain the urine sugar free. Harrop (19) states that the starvation method was attended with a considerable degree of success, particularly in the control of acidosis, and the mortality from the disease was appreciably lowered.

The diet of a juvenile diabetic should be a well balanced diet, adapted to the child's needs and tastes. It should not differ from the diet of other members of the family. Bader (4) states that the diet of the diabetic child should be as nearly as possible like the diet of the normal child. This diet is high in carbohydrate and low in fat. From two to three grams of protein per kilogram of body weight must be allowed. The caloric distribution should be, roughly, from 12 to 15 per cent of the calories as protein, from 30 to 35 per cent as fat, and from 45 to 55 per cent as carbohydrate. Enough food must be given to permit normal increments of growth and gain in weight. Obesity must be avoided. Insulin may be necessary to maintain the patient sugar free. Such a diet furnishes a factor of safety in uncompensated cases because of the excess of carbohydrate. It may be a factor in the few reactions to insulin. Fat depresses the efficiency of insulin. The high carbohydrate, low fat diet improves tolerance. The children are satisfied and do not steal food.

Bader (3) advocates the diet high in carbohydrate but low in fat as compared with the older and standard diets formerly employed in the treatment of juvenile diabetes. Specifically two to three grams of protein per kilogram of body weight are allowed in his cases unless the child is considerably underweight and undersized. He states that the question of the amount of food in calories to be given to a particular diabetic child varies as in the normal child according to its individual needs.

The protein needs are determined on the basis of what one considers normal weight for a nondiabetic child of a specific age. The amount of fat in grams should be approximately equal to that of the protein and the remainder of the total calories is furnished as carbohydrate.

During the process of desugarization and stabilization it often becomes necessary to transfer a few grams of carbohydrate from the breakfast to the lunch or do just the opposite as the fractional distribution cannot remain absolute. This is necessary in order to render the child sugar free.

Breakfast two-fifths, lunch one-fifth, and dinner two-fifths is a trial arrangement of diet suggested. A child occasionally has to have food between meals in order to prevent hypoglycemic reactions. There is often no other way of preventing these reactions except by giving this extra food at a specific time between meals. Where possible it is preferable not to give food between meals.

The diets arranged by Bader are high in carbohydrate and low in fat. Two to three grams of protein per kilogram of body weight are allowed unless the child is considerably underweight and undersized. An equal number of fat grams is given. The balance of the total calories required is furnished as carbohydrates. The question of the amount of food in calories to be given to a particular diabetic child varies as in the normal child according to its individual needs. One must be guided by the child's response in growth and gain in weight.

The following arrangement is suggested for a female seven years of age weighing 21 kilograms with a height of 125 Cm. (The normal weight for this child is 23 kilograms).

Two and one-half grams of protein are allowed per kilogram.

$$23 \text{ kilograms} \times 2\tfrac{1}{2} \text{ grams} = 57\tfrac{1}{2} \text{ grams}$$

Sixty grams may be used in an attempt to calculate in even numbers. The same amount of fat is used.

The total calories for the girl aged seven years is seventy-six calories per kilogram.

$$23 \text{ kilograms} \times 76 \text{ calories} = 1{,}748 \text{ calories}$$

The total calories minus the protein plus the fat calories is the sum of calories from carbohydrate alone.

Protein	= 60 grams	x 4 calories per gram	=	240	calories
Fat	= 60 "	x 9 " " "	=	540	"
				780	"

The total calories minus the protein plus fat calories leaves 968 calories to be supplied by carbohydrate. This number of calories must be divided by 4 calories per gram to determine the number of grams of carbohydrate in the diet.

The diet; carbohydrate, 240 grams; protein, 60 grams; and fat, 60 grams can conveniently be divided into three meals per day as suggested:

		Carbohydrate	Protein	Fat
Breakfast	(two-fifths)	96 grams	24 grams	24 grams
Lunch	(one-fifth)	48 "	12 "	12 "
Dinner	(two-fifths)	96 "	24 "	24 "

Jamieson suggests that the important foods used in the high carbohydrate low fat diet are bread, cereals, vegetables, a wide range of fruits, and lean meat. (21) Milk is allowed as a beverage and takes the place of cream or tea and coffee with the older children. Butter in small quantities is the only fat used. Eggs are used only in limited numbers because of their fat and high cholesterol content.

In such a diet the antiketogenic-ketogenic ratio is so high that ketosis is much less likely to occur than with a high fat diet, even with the loss of considerable sugar in the urine and the children on this diet are more energetic than on previous high fat diets with a similar caloric value.

Sansum (46) recommends a diet high in carbohydrates. He states that on such a diet it has been found there is no difficulty in keeping patients sugar free and with a normal blood sugar. The patients are restored to a more nearly normal state of physical and mental activity. They are freed from the slightest traces of the acetone type of acidosis. The potatoes, milk, and fruits enable one to eliminate the acid-ash type of acidosis believed to have been a cause of the high incidence of blood vessel disease. The diets are more palatable. The patients lose their craving for forbidden foods, especially for the carbohydrates. A somewhat lower caloric intake is apparently required for full maintenance. These diets are cheaper because they contain no special foods and much less of the expensive fats, such as cream, butter, and olive oil. Such diets should afford the patients the best opportunity for partial recovery.

In a carefully conducted study of the protein needs of diabetic children between the ages of four and fourteen years on relatively high fat, nonketogenic diets, Bartlett found that from 0.6 to 1.0 grams per kilogram of body weight was sufficient to maintain a positive nitrogen balance and to allow normal growth and development, so long as the total requirements were fulfilled. (36)

In a group of diabetic children diets were used by Bartlett which differed only slightly from those reported in detail by Newburgh and Marsh. (6) Definite metabolism periods were marked off, during which food nitrogen, stool nitrogen, and urinary nitrogen determinations were made. Daily weights and bimonthly measurements of height were recorded.

The patients were placed at first on a low caloric diet with only 0.6 to 1.0 gram of protein per kilogram of body weight. When the urine became sugar free and the blood sugar fell to a normal fasting level of 80 to 120 mgm. per hundred cubic centimeters, nitrogen studies were begun. After a week or two the diet was gradually raised in calories by increasing the fat content, and to a lesser degree, the carbohydrate content of the diet, until nitrogen metabolism reached a minimum. The patients were then studied over periods varying from four to eight months, their protein intake being kept at a constantly low level. It was possible to demonstrate the protein-sparing action of the ingestion of fat which has been noted by Thomas and reported by Petrén. Patients were kept in bed on sub-maintenance diets and allowed full activity on maintenance regimens.

As the caloric requirement was fulfilled in each case, the child came into positive nitrogen balance and began to gain in weight. The nitrogen equivalent of the protein intake was constant at 3.5 grams. Feeding a low protein, high caloric diet in diabetes mellitus maintains nitrogen metabolism at a minimum, decreases the available glucose in the diet, and decreases the tendency toward the development of ketosis and hyperglycemia.

In diabetic persons with a carbohydrate intake much below forty grams per day, with liberal amounts of fat, a very low nitrogen metabolism may be maintained over long periods. It is true that these are diabetic persons, but it does not seem probable that there is any difference in this phase of metabolism between the normal and the diabetic organism.

The acceptance of the low total caloric intake in the dietetic management of diabetes mellitus in contrast to the older overfeeding has increased the importance of an accurate knowledge of the minimum amount of protein that will maintain nitrogenous equilibrium in the diabetic patient.

The ultimate effect of long continued gradual loss of body nitrogen is not known, but it seems probable that such a condition is very undesirable. The subject whose nitrogen excretion is constantly higher than his nitrogen ingestion is certainly suffering for want of one of the most important of the tissue repairing elements, and a diet so arranged as to induce this negative balance, even though not lethal, must produce a severe grade of inanition. The normal subject may be maintained in nitrogen balance on less that 0.66 grams protein per kilogram of body weight, provided the total caloric intake is sufficient to supply heat and energy. (41)

The urine in diabetes may contain more nitrogen that that of any other disease. The French called this condition azoturia. Von Noorden (1907) demonstrated that this is due to the large nitrogen content of the diabetic's diet, either because of his own tendency to replace with protein the carbohydrate calories lost in the urine, or because of the very high protein content of the contemporary diabetic diet.

In mixed diets carbohydrate and fat are equally effective in sparing protein and of equal value as fuel for work. Carbohydrate may not be entirely replaced by fat, however.

Some patients with diabetes mellitus are more dependent on fat as a source of energy than are normal subjects, it is tempting to try to explain the hyperlipoidemia that is so common in this disease on the basis of some theory that assumes a relationship between the amount of fat in the food and the percentage of lipoids in the blood. (34)

Jonas (23) states that when carbohydrate tolerance is reached before the desired caloric requirement is furnished fat may be increased in the diet to the maximal limit, according to the following equation:

$$F. = 2\ C.\ \text{plus}\ 0.5\ P.$$

He also believes that appearance of diacetic acid in the urine in more than occasional traces demands a diminution of the fat in the diet.

Joslin suggests a relation between the high protein, fat diets of former days and the high degrees of lipemia reported, and states that "with restricted diet, particularly of fat, the blood fat rapidly falls."

Priessel and Wagner advocated a diet high in fat; from one hundred and twenty-five to two hundred grams a day. (14) Lowering the intake of fat reduces the caloric intake somewhat, but no harm results. Wagner reported adequate growth and development in his children on diets high in fat and did not place any emphasis on the presence of acetone. Most authors feel that a diet high in fat raises the insulin requirement over a certain period, while a diet containing a moderate amount of carbohydrate and fat does not. A diet high in fat raises the body weight which according to Joslin, increases the severity of the diabetes. (25)

Weintraud demonstrated conclusively as long ago as 1893 that fat fed to the diabetic subject was very powerful in saving his protein. (6)

Marsh and Waller (34) report the case of a three year old American boy who entered the hospital March 6, 1922 with diabetes, which had its onset in June, 1921, when the patient was two years of age. His father's brother had diabetes. The diagnosis was made very soon after the onset of the symptoms, and rigorous dietetic treatment under the supervision of very competent physicians failed to control the glycosuria. During most of the time between the onset and his admission to the hospital, his diet contained about forty grams protein, thirty grams fat, and twenty-five grams carbohydrate, about five hundred and thirty calories. His urine was sugar free at times during the first few weeks, but had not been at any time during the several months just previous to admission. His weight had fallen from thirty-two to twenty-nine pounds. Examination was essentially negative. On a diet containing protein, 8 grams; fat, 40 grams; and carbohydrate, 6 grams, he became sugar free on the twelfth day. His diet was increased to include protein, 15 grams; fat, 55 grams; and carbohydrate, 10 grams, without return of glycosuria. This allowed 4.2 grams fat per kilogram of body weight. The blood lipoids, which were slightly high at first, had fallen to a normal level by the thirty-third day.

This case suggests that the assumption diabetic hyperlipoidemia is dependent on the excessive ingestion of fat is unwarranted.

Himsworth (20) believes that the fat diet decreases sugar tolerance, retards and diminishes the action of insulin upon the blood sugar, prevents or delays the progressive improvement of sugar tolerance which occurs on injection of consecutive doses of glucose, and impairs the ability of insulin to diminish the hyperglycemia following intravenous injection of glucose. He states that fat diets and starvation diminish the susceptibility of an animal to insulin while carbohydrate diets and administration of glucose increase the susceptibility to insulin.

The metabolic problem in a child suffering from diabetes mellitus is far more difficult than that in the adult, since in the child one must provide not only for maintenance but also for growth. (29) It is a nice problem to accomplish this and at the same time to preserve the carbohydrate burning function of the body.

With the advent of insulin, the prospects for the future of the child with diabetes brightened. It seemed to mean that one could give sufficient food to sustain normal life and to keep the patient sugar free. Formerly it had been necessary to rely on reduced diet or on starvation.

The idea from which Banting's work originated presented itself from reading an article written by Moses Barron in Surgery, Gynecology, and Obstetrics, in the November issue of 1920. In this article which deals with the pathological changes of the pancreas following blockage of the pancreatic duct with gallstones, Barron points out the analogy between such degeneration and that which occurs following the experimental ligation of the pancreatic ducts in animals. (32)

Banting commenced work by ligating the pancreatic duct in a number of dogs. An interval of from seven to ten weeks was allowed for degeneration of the acinous tissue to occur. The dogs were then chloroformed and the degenerated remnant removed. Histological sections of this material showed replacement of the acinous cells by fibrous tissue. The degenerated remnant was cut into small pieces placed in ice-cold Ringer's solution, frozen, macerated and filtered. Depancreatized dogs, within twenty-four hours after the operation developed a high blood sugar, about .250 per cent. Second or third day blood sugar .300 per cent. Frequently .450 per cent in five to six days. The urine contained persistently large amounts of sugar. Acetone bodies derived from the animal's own body fat were present in slight amount.

The acinous, but not the insular cells became degenerated in seven to ten weeks after ligation of the pancreatic ducts. (5)

On July 31, 1921, the first degenerated pancreatic gland extract was injected into a diabetic dog. This injection was followed by a reduction in blood sugar from .20 to .11 in one hour. The animal became sugar free and was found to retain a larger amount of injected glucose than on a previous day when glucose alone had been given.

Lageusse (32) found that a comparatively larger number of islet cells were present in the pancreas of the fetus and the newborn than in adult animals. Attempts were made to keep depancreatized dogs alive by administering the extract.

The main object in November, 1921 was to obtain a means of chemical extraction of the active principle which would destroy, precipitate, or leave undissolved the deteriorating or toxic elements of the acinous cells.

In January, 1922, Collip was able to fractionally precipitate the active principle, and by this procedure was able to obtain a more refined extract of the whole gland.

All patients, whether mild or severe diabetics, are greatly benefited by insulin treatment, certainly enough to make it quite worth while for them to continue treatment. (13) The clinical change in children seems to be more obvious and quicker than it is in adults. The first change is mental. The next striking change is the skin, hair, etc., their return to normal texture and tone, the disappearance of eruptions and infections, and finally the gain in weight and ability to do so. An almost constant skin finding is the difficulty in inserting the needle at first. Within three weeks the needle passes through the soft skin easily.

In teaching children to give their own injections it is best to wait until the tough skin texture so frequently encountered in the beginning becomes soft.

If a diabetic patient is kept on a constant diet somewhat above his carbohydrate tolerance, with other conditions of life particularly exercise, also constant, the amount of sugar excreted nevertheless will vary from day to day. (37) When frequent samples of urine are examined, the excretion of sugar will be found to vary somewhat, independently of the meals. Some meals are followed by an immediate glycosuria, while others are followed by a slight increase or none.

The liver has been regarded as the body's chief storehouse of carbohydrate. Its blycogen content has been thought to express the balance between the supply of, and demand for carbohydrates in the body. Somewhat contrary to this simple view, Forsgren has recently shown that the liver is no such passive storer of glycogen, but a rhythmically functioning organ, alternately storing glycogen and secreting bile. A maximum amount of glycogen is present in the liver in the small hours of the night and early morning and a minimum is present at noon.

In addition to the daily rhythm of the function of the liver, there are, no doubt, periods of shorter and longer duration. In the excretion of sugar of diabetic patients on a constant diet, a regular periodicity can also often be traced, spanning three, four or five days.

Susceptibility to insulin varies with the functional stages of the liver and its glycogen content. In patients with severe diabetes treated with insulin in whom insulin shock had previously been observed, the latter regularly appeared at a time of day when reduced susceptibility of nourishment could be ascertained. Insulin should be administered with due regard for the endogenous rhythm, and not for meal hours.

The inner aspect of the thighs or the legs is a convenient location for injection of insulin. The site should be changed frequently; alternate. The injections must be given subcutaneously. (38) The injection of insulin adds to the distress of the parent. (21)

The urine becomes sugar free comparatively early, always depending upon the amount of insulin used. (13) The first marked change is the lowering of the specific gravity. The blood sugar is quickly reduced but even though the urine is sugar free a blood sugar higher than that generally concluded to be the spilling point is frequently found by the Folin method.

A dietary plan such as Bader suggested, p. 17, requires the administration of insulin at least twice daily. Although larger amounts of insulin are necessary in many children on this type of diet, the insulin can be made to accomplish more because more grams of carbohydrate are metabolized per unit of insulin on the higher carbohydrate, low fat diets. Bader (3) gives insulin twenty to thirty minutes before breakfast and twenty to thirty minutes before dinner. Occasionally he finds it advantageous to lengthen the interval between the insulin and the meal to forty-five minutes or one hour. This is done by giving the insulin earlier. The omission of a dose of insulin is inexcusable and dangerous but the time chosen for the injections may vary with the individual child. Sometimes it becomes necessary to administer a third dose of insulin at 1 or 2 A.M., in order to keep the patient sugar free during the night. The extra dose is required if the disease is severe, or has lasted two or three years or more and has been poorly controlled. There is an economic advantage in three doses daily, because it reduces the total insulin required for twenty-four hours. It also reduces the amount of insulin necessary per dose and thus reduces the likelihood and frequency as well as severity of insulin reactions.

Joslin states that diabetic children are in good condition since the advent of insulin but few in whom the disease is of long duration are sugar free throughout the entire twenty-four hours. (28) Most commonly glycosuria appears in them after breakfast but clears before noon. The best means suggested to prevent a forenoon glycosuria is to administer insulin an hour before breakfast or, if the urine is not sugar free on rising, to have the patient take from 2 to 5 units on retiring the preceding night, so that he awakens with glycogen stored in the liver and thus begins the day mildly diabetic. With glycogen in the liver the diabetes is never severe. Additional aids are a low content of carbohydrate at breakfast and a few minutes of exercise before it.

To determine the total insulin, the total available carbohydrate in the diet must be computed. This is all of the carbohydrate plus 58 per cent of the protein and 10 per cent of the fat. (3) The total carbohydrate in a diet made up of 240 grams of carbohydrate, 60 grams of protein, and 60 grams of fat is 280 grams. One unit of insulin is allowed for five grams of total available carbohydrate. A unit of insulin is the amount of active principle required to reduce the blood sugar of a normal rabbit, which has been starved eighteen hours, from its normal level of approximately .123 per cent to .045 per cent. Although there is a slight variation in the strength of the unit, it is equivalent in a moderately severe diabetic to about 2.5 grams of glucose. (32) In the case discussed, p. 17, 57 units of insulin are required. Three fifths of this can be given as breakfast dose (34 units); and two-fifths as dinner dose (23 units).

The final distribution of the carbohydrate in the diet when the patient is stabilized and the dietary adjustments have been made is approximately as follows:

	Carbohydrate	Protein	Fat
Breakfast	81	24	24
Lunch	63	12	12
Dinner	96	24	24

It requires two to four weeks before the child is finally stabilized.

Robertson (39) calculated, in a large group of collected cases, the ratio of potential carbohydrate in the diet to the insulin required to keep the urine sugar free. He calls this the C/I ratio. It can be used for patients of any age and on any diet of the low carbohydrate type. The index of severity is the ratio of the potential carbohydrate of the diet to the insulin required to keep the urine sugar free, in the absence of infections or toxemia.

When the C/I ratio is between 1.5 and 2 the patient is secreting little or no insulin. Children tend in time to get the ratio 1.5, after this they remain constant.

The formula used to estimate the potential carbohydrate of the diet is:

$$C. = 0.6 P.$$

This is an approximation of the formula

$$C. = 0.58 P. \text{ plus } 0.1 F.$$

If C. = 40, P. = 75, F. = 100

$$\text{Potential } C. = 40 \text{ plus } 0.6 \times 75, = 85$$

Collins and Grayzel found the glucose insulin ratio of particular value in indicating the course of the disease. (10) They determined this ratio by dividing the amount of glucose utilized by the amount of insulin required to keep the urine sugar free.

There seems to be evidence that certain patients gain carbohydrate tolerance on insulin treatment as indicated by a tendency for them to need less insulin to metabolize their food as time goes on. (38) The patient's tolerance is established by estimating the degree of glycosuria and acidosis, the blood sugar level, and the response to a maintenance diet. (10) Newcomb (39) suggests that in determining the tolerance, 1 unit of insulin is considered sufficient to burn 1 3/4 grams of glucose; the number of units of insulin administered is multiplied by 1 3/4 and the product in grams subtracted from the total glucose of the diet, the remainder being the amount of glucose metabolized, where the urine is sugar free.

Collins and Grayzel (10) suggest a method for establishing a patient's tolerance which consists in determining the degree of glycosuria on a stated test diet, the degree of acidosis, the height of the blood sugar response to the oral administration of a definite amount of carbohydrate.

When a patient ingests a stated amount of available dextrose in the diet and excretes a definite amount of dextrose in the urine, then the difference between the two figures represents the amount consumed, whether oxidized or stored. This is a measure of the patient's ability to utilize sugar. When, however, the patient requires a certain amount of insulin to aid in the utilization of the sugar, a more accurate index of the patient's tolerance would seem to be established by determining the ratio of the dextrose utilized to the amount of insulin administered. This ratio is called the dextrose-insulin quotient. Any one quotient may have a possible error of plus or minus 25 per cent.

The studies of Collins and Grayzel of ten ambulatory diabetic children over a period of two and one-half years indicated that there is no clear evidence of progressive improvement in the sugar tolerance of a diabetic child while under dietetic and insulin management. The methods employed in the course of treatment were based on the fundamental physiologic requirements of the growing child, the growth, activity, and well being of the patient being taken into account. These authors are compelled to disagree with conclusions reported in the literature that prolonged insulin therapy improves the patient's tolerance.

Cowie and Parsons called attention to the effect of infections (measles, chickenpox, etc.) on the consumption of insulin. (38) In some cases, it required three or four times as much insulin to metabolize a given amount of carbohydrate as it did before the infection was present. They showed that there is not any determining factor for the amount of insulin necessary during an infection. The amount must be governed by the amount of sugar in the blood and in the urine.

Netzley mentions an interesting observation in treatment of diabetes with insulin in that most children show cessation of weight gain when they reach the weight for their age and height.

PROGNOSIS AND COMPLICATIONS

The prognosis in juvenile diabetes is dependent upon adequate early treatment and every case merits careful supervision.

In the past diabetes was considered a progressively deteriorating disease ultimately approaching a total diabetes. With the discovery of insulin hope was aroused that this spectre would disappear, and many children showing great gains in tolerance have been reported.

It is generally recognized that infection is an important factor influencing the mortality statistics of diabetes mellitus. (42)

Robertson (44) believes that diabetes in children is usually a progressive disease, and that after each of the infections from which all children suffer, the insulin requirement becomes permanently higher, even if there is a slight remission during convalescence. He states that diabetic children can be kept healthy with insulin even if the disease is of long standing. It is possible that the severe cases may have no power of secreting insulin, or so little as to be clinically negligible.

Harrop states that diabetic children usually do very well on insulin and that it is quite possible that it has other beneficial trophic effects besides its action on the carbohydrate metabolism. (19)

Forty-one of fifty-one of Joslin's series remaining alive from the Allen era (1914-1922) are of normal weight or above weight for their height. If so large a proportion of the emaciated and underfed preinsulin treated children can attain normal growth, he believes there should be little difficulty for those in whom insulin is given at the onset as diabetic children resist all types of infections with proper adjustment of diet and insulin. (28)

The death of a diabetic child is almost invariably due to the conditions which cause coma. Diabetic coma is a gradually deepening stupor developing in a diabetic patient and is one of the most serious complications. (11)

The prevention of the advent of coma constitutes the treatment of diabetes and is accomplished by bringing about the combustion of sugar in the body and in this way the simultaneous combustion of the ketone acids, with the liberation of the bases bound by these acids. Insulin will do this. (45) The menace of acidosis and coma, in a case of diabetes is due to the fact that in this disease there is present, especially in children, a lessened ability on the part of the system to utilize fat.

According to John (22) abdominal tenderness can frequently be elicited before the child drifts into unconsciousness.

Ross (45) states that when the blood and other tissues and fluids of the body contain an overwhelming amount of two acids, beta-oxybutyric acid and aceto-acetic acid, a train of symptoms supervene which are classified under the term, acidosis. These symptoms are hyperpnea, vomiting, evidences of anhydremia, increasing restlessness and irritability, gradually or rapidly changing to somnolence or coma. Fever is not an accompanying symptom of diabetic coma (22).

The differential diagnosis in the presence of coma may cause at times some difficulty, or require time for the clearing up of the problem. Blood counts are high in diabetic coma because there is dehydration with concentration of the blood. When dever is present one should look for infection, otitis media, or a gastro-intestinal upset. (22)

Ross (45) believes that as soon as the diagnosis of coma is established insulin should be administered subcutaneously or intravenously or both. On the basis of it requiring one unit of insulin to bring about the combustion of from one and one-half to two grams of glucose, the amount necessary can be estimated when the percentage blood sugar is known. 60 per cent of the body is fluid. This percentage of the weight in kilos indicates the amount of fluids present. This multiplied by the percentage of sugar present is the number of grams of sugar in the body. The normal amount of sugar present in health should be deducted from this. The result is the excess.

In Rabinowitch's experience no uncomplicated case of diabetic coma has as yet failed to respond to insulin treatment. (42) He believes that diabetes occurring in childhood represents a pure type and it is in these patients that the maximum improvement with insulin may be expected.

Although it is known that the complications associated with diabetes in the adult can occur in the child, Joslin and White have found that it is the diabetic child treated with the inadequate methods of yesterday who has developed cataracts and arteriosclerosis. Joslin attributes the appearance of these complications, at least in part, to the high fat content of the diet with which many of his patients formerly were treated. (26) Allen (2) says that arteriosclerosis is demonstrable in every case past middle life in which glycosuria has been present ten years or more. According to Joslin (26) diabetic children of today constitute an experiment and when one hundred diabetic children have lived a decade and reports have been published about them, which state the presence or absence of arteriosclerosis in conjunction with the percentage of sugar in the blood, one shall be in a better position to reach such a conclusion. He does not believe that a hyperglycemia up to 0.25 per cent is particularly harmful to a diabetic provided the urine is sugar free, because this is proof that he is not eating carbohydrate uselessly, and carbohydrate is our standard food.

Fear of hypoglycemia should not prevent any one from benefiting from insulin when it is needed. According to Allan and Wilder (1) to deny insulin to a patient in danger of diabetic coma is inexcusable.

Joslin considers it astonishing that diabetic children have so few reactions and so seldom simulate them. It is his belief that deaths from insulin reactions are very rare. (28)

According to Nicely the symptoms of hypoglycemia are; weakness, extreme hunger, trembling, sweating, and collapse.

He uses corn syrup or glucose solutions to combat hypoglycemia, or allows patients to carry or keep near at hand an orange or piece of candy. (40) The ordinary insulin reaction can be quickly checked by the ingestion of sugar or other food. (1)

Convulsions as a manifestation of diabetes have been reported many times, particularly in the older literature. In the cases occurring in children confusion in the diagnosis has occurred chiefly in differentiating between hypoglycemic convulsions and epilepsy. (24) Jordan believes it wise in such patients to change the dosage of insulin so that hypoglycemia does not occur, even though slight glycosuria results and then make a careful and prolonged study of the patient to clarify the diagnosis. He considers recurrent attacks of convulsions without subsequent aphasia, mental derangement or muscular paresis and without other obvious cause epilepsy.

McQuarrie states that no matter what the true mechanism of its action may be, the low carbohydrate, relatively high fat diet, together with restriction of the total water intake, offers the most effective and most promising type of therapy for the epileptic child. (36)

Harris (17) examined diabetic children radiographically and found that multiple lines of cessation of growth were found to be a constant feature whenever the disease was of long standing. He found the lines of arrested growth persisting in the bones adjoining joints with a movement essentially nonaxial (ankle or knee). The bony lines were absorbed rapidly at the wrist and elbow in accordance with the rapid remodeling in an area subjected to bending strains and torts.

In twenty-two months ending July 1, 1928, the total mortality among 303 diabetic children of the Joslin series was six, or 1 per cent a year. In the six year period between August, 1922, and July, 1928, the total mortality for 337 diabetic children was thirty-six, or 2 per cent a year. (28)

Lawrence (30) found that in a group of 59 hospital cases there were six deaths or a per cent living of 90. Of his private patients in a group of 69 there was one death or a per cent living of 99. These figures do not take into account the survival time in each individual case. Some of these children have survived ten years, others have only been a year or two under his treatment. Lawrence believes that to secure such good results continuous care and treatment are necessary and in practically every case insulin injections must be a part of the routine.

In a group of 18 patients with diabetes who attended Addenbrooke's Hospital between 1925 and 1933, and who at the time of onset were less than fifteen years old sixteen survive. (9) In five the disease began before 1927, and until that year their treatment with insulin was intermittent and insufficient. All the sixteen who survive were under regular supervision from 1927 until May, 1934. The cases were unselected and comprised all the diabetic children attending between 1927 and 1933. They were mostly drawn from an illiterate class, and although they themselves were usually of the more intelligent type, it was difficult with the organization available to teach them more than a few essential facts about the management of their disease. The diabetes came on in one case at three, in one at four, in one at six, in three at seven, in two at nine, in one at ten, in one at eleven, in three at twelve, in four at thirteen, and in one at fourteen years. In those cases with a longer duration than five years insulin treatment was often insufficient to control the disease and the diet was often very restricted.

In a group of 8 juvenile diabetics attending the Diabetic Clinic of the University of Nebraska College of Medicine Dispensary from 1930 to 1935 there have been but two deaths. Both of these patients died at the Douglas County Hospital and the apparent cause of death was myocardial degeneration. One of these was a male thirteen years of age and death followed coma. The diabetes demonstrated possibility of control but there was lack of co-operation. Tap water was submitted for urine specimens and food was taken outside of the diet arranged. In the other case death occurred at the age of four years and seemingly followed an infection. The diabetes in this particular case resisted control and there was lack of co-operation by the patient and his family due to discouragement. There seemed to be too great a flexibility in the reaction to insulin so that frequent alternations from insulin shock to hyperglycemia occurred.

Of the six remaining cases in the University Dispensary series in one there is xanthochromia. In another case, a male four years of age, there is a flexibility in the reaction to insulin. One case in the series is not difficult to control but there is lack of co-operation. One case which entered the clinic as a pseudodwarf one year ago has already gained two inches in height and has shown a satisfactory gain in weight. This patient is now under control and is co-operating. The two remaining patients are progressing satisfactorily but in one of these it is difficult to secure co-operation.

SUMMARY

There is no doubt but that heredity plays a part in the production of the defects of carbohydrate metabolism giving rise to glycosuria and diabetes in many instances although the high carbohydrate diet and the influence of infection must not be forgotten as possible etiological factors of considerable significance. The significance of overgrowth is puzzling. Overheight may be the result of optimum nutrition or infections with their subsequent gains in length. Overgrowth may be associated with hyperactivity of the other glands of internal secretion.

Pathological findings in the pancreas of juvenile diabetics are not sufficient to account for the marked disturbance in function.

Diabetes mellitus presumably represents hypoactivity of the pancreatic islets and children with this condition can be expected to show high and prolonged blood sugar curves. Fat alone is oxidized for the maintenance of the body when carbohydrate metabolism is impaired.

Before the appearance of glycosuria it is difficult to prove that diabetes exists although certain symptoms are frequently mentioned. Growth in height in children with diabetes mellitus diminishes or stops completely depending upon the severity of the case. The mental age of diabetic children is usually considerably above their chronological age.

Diet, exercise, and insulin are important factors in the treatment of juvenile diabetes and adjustments must be made to meet the problems in each individual case as they arise. The matter of co-operation is greatly influenced by the ability of the clinician to tactfully meet distressing situations as such appear. Maximum co-operation can be expected when the diet and life of the patient is as nearly as possible like that of the normal individual. All patients, whether mild or severe diabetics, are greatly benefited by insulin treatment.

The prognosis in juvenile diabetes is dependent upon adequate early treatment. Death of a diabetic child is almost always due to the conditions which cause coma and with careful supervision and maximum co-operation this complication can be avoided.

JUVENILE DIABETES

BIBLIOGRAPHY

(1) Allan, Frank W., and Wilder, Russell M.
Causes of Failure in The Treatment of Diabetes of Children
J. A. M. A. 94:147, Jan. 1930

(2) Allen, Frederick M.
The Dietetic Management of Diabetes
Am. J. M. Sc. 167:554, Apr. 1924

(3) Bader, George B. Observations on The Management and Treatment of Juvenile Diabetes
J. Pediat. 4:77, Jan. 1934

(4) Bader, George B. The Management and Control of Juvenile Diabetes Am. J. Dis. Child 46:445, May 1933

(5) Banting, F. G., Best, Charles H., and MacLeod, J. J. R.
The Internal Secretion of The Pancreas
Selected Readings in The History of Physiology, p. 306,
Charles C. Thomas, Pub.

(6) Bartlett, Walter M.
Protein Requirement as Determined in Diabetic Children
Am. J. Dis. Child. 32:641, Nov. 1926

(7) Bowen, Byron D. Economic Results of The Modern Treatment of Diabetes J. A. M. A. 95:565, Aug. 1930

(8) Cammidge, P. J. Diabetes Mellitus and Heredity
Brit. M. J. 2:738, Oct. 1928

(9) Cole, Leslie Diabetes Mellitus in Children
Lancet 1:1002, May 1934

(10) Collens, W. S., and Grayzel, H. G.
The Management of The Ambulatory Diabetic Child
Am. J. Dis. Child. 38:275, Aug. 1929

(11) Conlin, Frank Instructions for Diabetic Patients, p. 19,
Pub. at Omaha, Nebr. 1931

(12) Cori, C. F. The Fate of Sugar in The Animal Body
J. Biol. Chem. 66:691, Dec. 1925

(13) Cowie, D. M., and Parsons, J. P.
Clinical Observations on the Use of Insulin in the Treatment of Diabetes in Adults and Children with Particular Reference to the State of Hyperinsulaemia (A Consideration of Insulin and Renal Glycosuria)
Tr. Am. Pediat. Soc. 35:217, Apr. 1923

(14) Fischer, Alfred E. The Treatment of Juvenile Diabetes
Am. J. Dis. Child. 38:323 Aug. 1929

(15) Folin, O., and Svedberg, Andrea
The Sugar In Urine and In Blood
J. Biol. Chem. 70:405, Aug. 1926

(16) Gibb, William F., and Logan, Victor H.
Diabetes Mellitus (A study of one hundred and forty-seven autopsies)
Am. J. Dis. Child. 43:376, Mar. 1929

(17) Harris, H. A. Lines of Arrested Growth in The Long Bones of Diabetic Children
Brit. M. J. 1:700 Apr. 1931

(18) Harris, Seale Hyperinsulinism and Dysinsulinism
J. A. M. A. 83:729, Sept. 1924

(19) Harrop, George A., Jr.
Diet in Disease, p. 256,
P. Blakiston's Son & Co., Pub.

(20) Himsworth, H. P. Dietetic Factors Influencing The Glucose Tolerance and the Activity of Insulin
J. Physiol. 81:29, Mar. 1934

(21) Jamieson, Heber C.
The High-Carbohydrate Low-Fat Diet for Diabetic Children
Canad. M. A. J. 27:389, Oct. 1932

(22) John, Henry J. Diabetic Coma in Children
Am. J. Digest. Dis. & Nutrition 1:569, Oct. 1934

(23) Jonas, Leon, and Musser, John H.
An Outline of a Routine for Insulin Therapy Am. J. M. Sc. 167:586, Apr. 1924

(24) Jordan, William R.
Epilepsy and Convulsions in Diabetes
Arch. Int. Med. 52:665, Nov. 1933

(25) Joslin, Elliott P.
A Diabetic Manual, 5th ed., p. 177,
Lea & Febiger, Pub. 1934

(26) Joslin, Elliott P.
Arteriosclerosis and Diabetes
Ann. Clin. Med. 5:1061, June 1927

(27) Joslin, Elliott P.
Diabetes Mellitus, Reginald Fitz
Oxford Med. 4:146, 1921
(See ref. No. 34)

(28) Joslin, Elliott P., and White, Priscilla
Diabetic Children
J. A. M. A. 92:143, Jan. 1929

(29) Ladd, W. S. Growth in Children with Diabetes Mellitus
Am. J. Dis. Child. 32:812, Dec. 1926

(30) Lawrence, R. D. Prognosis of Diabetes in Children
Lancet 1:807, Apr. 1934

(31) Mackler, Harry S., and Fischer, Alfred E.
The Sugar Tolerance in Siblings of Juvenile Diabetic Patients
J. A. M. A. 103:240, July 1934

(32) MacLeod, J. J. R., and Banting, F. G.
The Antidiabetic Functions of The Pancreas and The Successful Isolation of the Anti-Diabetic Hormone--Insulin, Lectures No. I and III, p. 1 and 25
C. V. Mosby Co., Pub. 1923

(33) Marsh, Phil L., Newburgh, L. H., and Holly, L. E.
The Nitrogen Requirement for Maintenance in Diabetes Mellitus
Arch. Int. Med. 29:97, Jan. 1922

(34) Marsh, Phil L., and Waller, H. G.
The Relation Between Ingested Fat and The Lipemia of Diabetes Mellitus
Arch. Int. Med. 31:63, Jan. 1923

(35) McLean, Aubrey B., and Sullivan, Ruth C.
Dextrose Tolerance in Infants and in Young Children
Am. J. Dis. Child. 37:1146, June 1929

(36) McQuarrie, Irvine Protein Metabolism of Children on Diets Extremely Low in Carbohydrates
J. Nutrition 2:31, Sept. 1929

(37) Möllerstrom, Jakob Periodicity of Carbohydrate Metabolism and Rhythmic Functioning of the Liver, Their Significance in the Treatment of Diabetes with Insulin
Arch. Int. Med. 52:649, Nov. 1933

(38) Netzley, R. E. The Effect of Diphtheria Toxin on The Action of Insulin
Am. J. Dis. Child. 37:511, Mar. 1929

(39) Newcomb, Alvah L. Diabetes Mellitus in Children
J. Pediat. 4:617, May 1934

(40) Nicely, W. E., and Edmondson, C. C.
The Use of Insulin in Treatment of Diabetes Am. J. M. Sc. 167:570, Apr. 1924

(41) Petrén, Karl Low Nitrogen Metabolism with Low Carbohydrate Diet in Diabetes
J. Biol. Chem. 61:355, Sept. 1924

(42) Rabinowitch, I. M. Influence of Infection upon Reaction of Diabetic to Insulin Treatment
Canad. M. A. J. 14:481, June 1924

(43) Rabinowitch, I. M. The Cholesterol Content of Blood Plasma in Juvenile Diabetes
Arch. Int. Med. 43:373, Dec. 1929

(44) Robertson, H. E. W.
The Extent of The Pancreatic Lesions in Diabetic Children
Arch. Dis. Child. 7:83, 1932

(45) Ross, Fred E. Abolishing Coma in Diabetes, and its Treatment if Present
Penn. M. J. 34:365, Mar. 1931

(46) Sansum, W. D. The Use of High Carbohydrate Diets in the Treatment of Diabetes Mellitus
J. A. M. A. 86:178, Jan. 1926

(47) Warren, Shields The Pathology of Diabetes in Children
J. A. M. A. 88:99, Jan. 1927

(48) White, Priscilla Diabetes in Childhood and Adolescence
Chapt. V, p. 77, Lea & Febiger, Pub. 1932

(49) White, Priscilla The Future of The Diabetic Child
J. A. M. A. 95:1160, Oct. 1930

(50) White, Priscilla, Joslin, Elliott P., and Pincus, Gregory
The Inheritance of Diabetes
J. A. M. A. 103:105, July 1934

(51) Woodyatt, Rollin T.
Diabetes Mellitus
Cecil--A Text-Book of Med., 3d ed. p. 631, W. B. Saunders Co., Pub. 1933