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Diabetes mellitus in children

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SENIOR THESIS

DIABETES MELLITUS IN CHILDREN

APRIL 1931

M.D.VEST

DIABETES MELLITUS IN CHILDREN

GENERAL CONSIDERATIONS

Diabetes Mellitus in children has special features, but on the whole its manifestations in children are much the same as those found in the adult. "The disease is characterized by an increase of sugar in the blood and the excretion of sugar in the urine; it is dependent upon disease of the pancreas, particularly of the islands of Langerhans whose secretion, insulin, not only promotes the conversion of glucose into glycogen and the deposition of the latter in the liver and muscles, but also exerts an influence upon the conversion of protein and fat into sugar."

³⁵ Prior to the introduction of insulin, diabetes mellitus in children ran a rapidly progressive course, often proving fatal within six months after the symptoms had become sufficient to lead to a correct diagnosis. With rigid dietetic treatment and intelligent care it was occasionally possible to prolong the life of an older child for two or three years. However, the diet upon which life was sustained was inadequate for normal growth and development; consequently the typical diabetic child on dietetic treatment in the preinsulin days was much under nourished and stunted in growth if the mildness of his disease permitted his survival. ² Senator in 1872 declared the prognosis of diabetes in children hopeless and all treatment useless. Priesel and Wagner stated that all patients seen between 1912 and 1923 had died sooner or later from coma. Naunyn and von Noorden said there were few exceptions. Joslin regarded the condition in his living diabetic children as coma deferred.

³³ Insulin revolutionized the treatment of diabetes in patients of every age, but the most striking and encouraging results have been obtained in the treatment of the disease in children. ²⁰ Statistics show that the per cent of children in total deaths from diabetes is a great deal less than formerly. It is as it should be; the younger diabetics are living longer than the older diabetics.

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Now it is possible to supply the immediate metabolic requirements of these children so that they not only live, but live well on diets closely approaching those of normal children. However, a therapy should not be accepted as a completely achieved ideal form of treatment for children, no matter how great may be its advantages over methods previously in use, unless it restores their normal rate of growth and development.

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It is true that children comprise only 6-8 % of diabetic patients, but they deserve and are receiving unusual consideration and care because they are the pure diabetics. They are the cases which are uncomplicated by the degenerations of old age; they are the ones from whom we may expect to learn much as to prognosis, regeneration of the pancreas or possible cure, the diabetic complications of the skin, the eyes, the arteries and also of diabetic surgery, and ultimately of the diabetic causes of death if such exist. Joslin said that a child under one year of age developing diabetes is worthy of a medical endowment.

ETIOLOGY

Although we look to the child diabetic for the explanation of the cause of diabetes, as yet it appears that still less is known about the etiology in children than in adults. Joslin²² has always been interested in the hereditary factor; if on his first visit he failed to find diabetes in the ancestry, he made inquiries at subsequent visits, often obtaining the evidence later. The incidence of a diabetic heredity in a diabetic child increases with the duration of his disease and with the number of his relatives. Joslin found that an inherited predisposition existed in 17% of the patients who died, in 35% of the living, and in 44% of those children whose disease was over ten years duration. A consideration of the sources of error in such statistics puts further emphasis upon the hereditary factor; (a) Many people do not know the cause of death of all their ancestors. (b) Latent diabetes may not show up because the relative may die before reaching the age of highest incidence of diabetes. There are cases in which children show diabetes before the disease crops out in the parent. (c) The relatives of a diabetic child who has

died are no longer followed by the physician. Relatives should realize that at least one in three, probably every other diabetic child, and possibly all diabetic children are born with a diabetic tendency. These relatives should take warning and avoid obesity as they approach middle life.

If then, the hereditary tendency is such an important factor, the question naturally arises; Should a diabetic marry? Joslin²² says, "Yes, if they have proved themselves masters of their disease and have sufficient funds. Non diabetic persons with a diabetic heredity are far too common to make interdiction of marriage justifiable. The children of diabetic mothers treated with care during their pregnancies are large, attractive, and mentally precocious as are diabetic children themselves who are reared under good surroundings. Thus far we have not had a diabetic patient that married whose child developed diabetes, but of course such an instance is bound to arise sooner or later. Perhaps the child of a person with diabetes will make up in mind and physique for his deficient carbohydrate metabolism". He believes that girls should have had their disease ten years before assuming so much responsibility. Of course it is not desirable for a man with strong diabetic heredity to marry a woman with strong diabetic heredity, but after all, who would permit one to point out whom he should or should not marry and when or whether he should have children.?

There has been much statistical study from careful clinical observation on the characteristics of diabetic children at the onset and during their disease. Priscilla White³⁸ at Joslin's clinic in Boston found that overheight in the diabetic child is more common than overweight in the diabetic adult in the past history of the patient. Previous to insulin therapy, surviving diabetic children soon fell far below height as well as weight, and the fact that the diabetic child was originally tall for his age escaped notice. Using the standard of Holt, 87% of 100 diabetic children were found to be overheight at the beginning of their diabetes.

These children were of the public school class and of average racial mixture. They did not have an especially favorable environment for growth as evidenced by the fact that on first examination 4% had abscessed teeth, 44% had evidence of tonsil infection within 18 months of onset, and 64% had general adenopathy.

It is well known that growth may be accelerated or retarded by disorders of the endocrine glands. The intimate relation of diabetes to disorders of the glands of internal secretion other than the pancreas is impressive and should be recognized. The possible relationship of the pituitary gland to diabetes has become more convincing through the work of Dr. Harvey Cushing who demonstrated the frequent association of hyperactivity of the pituitary gland and depressed function of the internal secretion of the pancreas by the frequency of hyperglycemia and glycosuria in 100 of his acromegalic patients. The excessive growth found in the 87% of diabetic children may well be a phase of pituitary activity. Whatever the explanation may prove to be, it is significant that preceding the onset of diabetes in the child it is the rule to find for the age an excess of height.

This study at Boston stimulated other workers to closer observation of diabetic children. I.M. Rabinowitch²⁹ of Montreal; "Though height and weight measurements are made as a routine in our clinic for diabetes, we had not observed this phenomenon. On investigation of our cases we found forty overheight children out of seventy-one. It was also noted that the average rate of growth of these children after treatment was instituted was less than normal. From this observation alone it appeared that whatever the stimulus which produces diabetes in the the child may be, it also causes excess skeletal growth. This was further suggested by the fact that when all the children were grouped with respect to heights on admission to our clinic namely (a) those that were overheight and (b) those that were normal or underheight, the average rate of growth of those of the former group was distinctly less than those of the latter. The standards of normal were taken from

the seventh edition of Holt's Book, "Diseases of Infancy and Childhood," because that data is based on measurements made by ten different authors. The average rate of growth of the whole group after treatment was instituted was 82% of the normal. In those who were overweight on admission, the rate was only 75.6% as compared to a rate of 90.8% in those who were normal or underheight on admission. This data was compared with data compiled on seventy-one non-diabetic children chosen at random. Of the normal children those who were overweight when first observed continued to grow at an increased rate, 112.1% of normal rate; those normal children who were underheight or of normal height when first observed continued to grow at slightly above the normal rate. This shows that the diabetic group as a whole had decreased rate of growth after treatment was instituted and that whereas those diabetics who were overweight when first seen, had a growth rate of only 75.6% of normal after treatment had been started, the non diabetics who were overweight when first seen continued to grow at an increased rate of 112.1% of normal rate. The above findings suggest that whatever the stimulus is that causes diabetes in children, it is also responsible for excess skeletal growth. Considering the relationship between skeletal growth and the anterior lobe of the pituitary gland the question arises; Is diabetes occurring in children who are overweight, of pituitary origin? Of course this study is purely statistical and does not apply to any particular individual; the number of observations are small because in any one clinic the number of diabetic children is small. The results of this study are recorded, not because we are convinced that the findings will apply to a much larger series of cases, but in order that they may be tested by others with similarly available data."

The findings of other investigators are much the same but are not always given the same interpretation. Joslin²¹ and associates found that the rate of growth even with the use of insulin was less than normal but the diabetic child was often but little underheight for his age because he was overweight at onset.

Of course the promptness and adequacy of treatment is an important factor in the development of diabetic children. Sherrill,³⁰ in reporting 62 living cases found under his treatment that some patients had good growth in height when on insulin with reasonable diet. Ladd²³ reported 34 cases all of whom but four showed either overweight or overheight at the onset of diabetes. Boyd and Nelson¹⁰ who noticed the same to be true in their group report, " For the first few months after the dietary management has been established, the gain in weight is often out of proportion to the gain in height. If the management is adequate, growth of height is accelerated and the patients' proportions soon tend to approach the standard. The growth response of these carefully regulated diabetic children is greater than that of so-called superior groups of non-diabetic children. This would suggest that the present concept of the rate of normal development for a healthy child may not equal his optimum, and that this might be better approximated by careful dietary regulation throughout childhood." It may be true that a more careful dietary regulation in childhood would benefit the development of most children to such an extent that the standards of normal would be raised, but surely the large percentage of diabetic children who show overheight at the onset of diabetes are not tall for their age merely because of any superior dietary management. The decreased rate of growth of such children as compared with the rate of growth of overheight non-diabetics is also significant as pointed out by Rabinowitch. Spencer³³ of Boston found the growth of his diabetic children to be above normal at onset of the disease with a subsequent decrease in rate to 24% below normal. He studied the rate of growth during insulin treatment to determine if his patients were under optimum management for development. He considered the rate of growth a good index of adequacy of insulin dosage. After a roentgen study²⁴ of bone development in 68 diabetic children, Morrison and Bogan report; (a) Bone development is in advance of chronologic age in children with diabetes of recent onset. (b) Bone development is below the chronological age in children with diabetes of long duration.

standing . (c) Narrowness of shaft and thinness of cortex is characteristic in children with diabetes of long standing. (d) Bone atrophy occurs in some who develop diabetes before the ninth year, but not in those who develop the disease after they are nine years old. (e) Transverse striae of bones are found in a larger percentage of diabetics than normal children but they failed to associate a transverse line with onset of the disease - too often infection had preceded onset of diabetes with too short an interval to properly evaluate the relation of transverse lines to onset of diabetes. The above studies indicate strongly a causal relationship between rate of skeletal growth and diabetes. The discovery of this phenomenon may be an important step in determining the etiology of diabetes.

Joslin²⁰ points out the striking parallel that exists between the beginning and the end of sexual activity and the onset of diabetes. He associates this idea with the fact that the influence of the internal secretion of the glands of sex on skeletal growth and body weight is best shown at two periods of life, puberty and menopause, the two periods when diabetes is most likely to show itself. Before the use of insulin it was noted that girls in whom diabetes began before menstruation the latter usually failed to appear. At present, the normal sexual development of a diabetic child at puberty is considered as an index of good or bad treatment. Subinvolution of the thymus and hypothyroidism are also considered, but little evidence has been presented.

Because infections are so abundant in children, it is difficult to identify an infection as the cause of the onset of diabetes. Syphilis, tuberculosis and emotional excitement seem to have no special significance. The etiology of diabetes is an unknown to be found; the evidence of extrapancreatic endocrine disturbance and the hereditary factor are worthy of continued study.

PATHOLOGY

Allen³ found in his partially depancreatized dogs a characteristic hydropic degeneration of cells of the islands of Langerhans. The dogs were potentially

diabetic but free from symptoms on limited diets. Overfeeding irrespective of quality of food, carbohydrate, protein, fat, resulted in active diabetes determined clinically by symptoms and pathologically by disappearance of the granules in the cells of the islands, swelling of the cells with fluid, and eventually disappearance of the islands. The rate of anatomic change varied with the clinical condition, but with unchecked severity of the diabetes a period of 4-7 days was generally required for development of the first positive vacuolation; maximum vacuolation was attained in four weeks; and in 6-8 weeks all beta cells had disappeared from the islands. Hydropic change was distinguished from the hyalin and other degenerations not only by microscopic appearance but especially by the fact that it was not primarily degenerative in nature but was produced solely by overstrain of the function of the cells by diets in excess of the assimilative power. Allen reported, "It is not in its beginning an expression of any injury or impairment of vitality of the cells affected, but it is purely a functional exhaustion comparable to the emptying of the acinar cells of the pancreas under the stimulus of secretion or of the chromaffin cells of the adrenal medulla under certain stimuli. A distinction here is that in the case of the Langerhan cells the exhaustion is carried to the point of anatomic destruction of the cells. The hydropic change is probably reversible within certain limits and even widely vacuolated cells may probably recover their former size and granulation provided the cell membrane has not burst or the nucleus become too badly degenerated. The demonstration of the hydropic change is important for ; (a) Its presence affords a positive microscopic diagnosis of active diabetes. (b) It completes the proof of the island theory of diabetes (c) It adds to the evidence of the essential identity of experimental and clinical diabetes (d) It explains the permanent lowering of assimilation in diabetes consequent upon excessive diets. (e) From a broader physiological standpoint it offers the only proved example of anatomic breakdown

of cells due to overstimulation of an internal secretory function.

The pathological characteristics found by Allen in experimental animals have not been observed in diabetic children. Shields Warren³⁶ autopsied ten diabetic children, one of whom was killed in an auto accident, all the others died in coma. "The pancreas was noted as small in most cases but the size varies considerably in non diabetics, and the pathologist vainly searching for some definite lesion in diabetes is apt to stress a small pancreas in a diabetic patient and to gloss over a large one. Experiments have shown that one fifth the normal amount of pancreatic substance is sufficient to prevent diabetes, hence minor variations in size are of little significance. In only one case was the number of islands reduced markedly and even this patient apparently had sufficient insular tissue to carry her almost four years after birth before symptoms appeared. She lasted only 1.9 years after onset of symptoms. The absence of degenerated islands or of foci of scar tissue that might represent the site of destroyed islands leads to the belief that the reduction of insular tissue is congenital rather than the result of disease. Varying degrees of congenital diminution in number of islands have been reported ranging from their complete absence to only a slight decrease. Estimation of their number is always difficult and probably never completely accurate. There is little pathologic change in either island or acinous tissue, though commonly reported in the old, and that present does not appear sufficient to account for the marked disturbance in function. Lymphocytic infiltration of the islands, found among children, is a lesion not encountered in older diabetic patients, and hyalinization of the islands, the lesions so typical in older persons, is not found in the young. Apparent pathologic changes of the pancreas are not present in most cases of diabetes in children. Any irreversible change in the insular tissue should be apparent on pathologic examination. The absence of demonstrable injury indicates that the disease in children is not ordinarily due to destruction of the island tissue, and the hope that function may be restored under the favorable circumstances of treatment is not beyond the realms of possibility."

Page and Warren²⁶ found at post mortem of a group of young adults, the striking feature of slight amount of pathology in the pancreas. Some showed reduction in the number of islands, others had sclerotic islands, still others had fibrosed or hyalin degenerated islands. "The outstanding pathologic change is evidence of disturbed lipid metabolism particularly as manifested in atheromatous changes in blood vessels. In one case only 12 years old the atheromatosis and changes in the internal elastic lamina were comparable to those in a man 50-60 years old. There was **also** further evidence of disturbed lipid metabolism as shown by the presence of lipid droplets. One case died of an infarct of the heart secondary to sclerosis and almost complete occlusion of the coronary arteries together with extensive atheromatous degeneration of the aorta. These cases of young individuals with extensive athero-sclerosis emphasize the danger which arterial disease presents to diabetics and calls attention to the need for considering lipid as well as carbohydrate metabolism of the diabetic. The pathology of the pancreas in young diabetics is almost invariably a disappointment to the morphologist. The younger the individual the less complicated his diabetes and the less likelihood there is of demonstrable anatomic change in the pancreas." Absence of definite pathologic changes is of prognostic value for it leads to the hope that irreversible changes in the pancreas may be avoided.

SYMPTOMS AND DIAGNOSIS

Diabetes does not develop over night. The onset of symptoms may be indefinite, gradual over a period of weeks, or rapid as measured in days. The only safe method is to examine urine routinely whenever a patient is seen, and consider a patient with glycosuria as diabetic until proven otherwise. Persistent glycosuria while the patient is in the hospital on a general diet with persistent high blood sugar (over 140 mg. fasting, over 160 mg. following meal) are usually sufficient for diagnosis. Some insist on a glucose tolerance test with typical diabetic curve before they will put the patient upon insulin therapy. Sherrill³⁰ writes; "The diagnosis in children is relatively easy since

the classical signs, polydipsia, polyuria, polyphagia and loss in weight are usually strikingly in evidence in contrast to doubtful diagnostic signs such as fatigue, weakness, and vascular degenerative processes as seen in the elderly. The most important diagnostic sign of diabetes in children is thirst; the benign glycosurias in children are usually not associated with changes in water balance, however any child with glycosuria must be considered diabetic until the contrary is proven." Smyth found that, "In infants and young children, diabetes is often ushered in with an acute gastro intestinal upset. Vomiting and diarrhea may be characteristic and the abdominal cramp-like pains may be of significance with regard to pancreatic involvement. With the subsidence of gastro intestinal symptoms, increased thirst and polyuria may persist and if the significance is not quickly recognized may lead to a rapid and fatal termination. Unlike in adults, a failing appetite may be associated with diabetes in younger children and parents are prone to ascribe emaciation which is a common finding in this disease to the failing appetite rather than to its true cause. Frequent polyuria as noted by bed-wetting or enuresis is often the first symptom noted. In general after seven years of age, the diabetic child's full symptomatology is similar to that of the adult. Some patients give a history of infection preceding the symptoms of diabetes, though as a rule, the damage from the infection is so severe as not to be relieved when the infection disappears. The accurate diagnosis of diabetes rests upon the glucose tolerance test by which other causes of glycosuria may be ruled out. "

Toverud³⁵ pointed out a source of error in blood sugar interpretation. "The small glycogen store in children which will tend to keep the blood sugar at a normal level for some time, sometimes obscures the findings somewhat and makes diagnosis uncertain. If the child for a few days before the urinalysis has taken little food, the urine may be sugar-free, and the fasting blood sugar may be normal even if the child is suffering from a true diabetes mellitus. The value of a glucose tolerance test is of particular importance in children .

A three year old boy sent to the doctor with symptoms of diabetes mellitus was found to have sugar free urine. The first day in the hospital he showed a normal fasting blood sugar and passed sugar free urine. The glucose tolerance test, however, revealed a typical diabetic curve. The boy died one month later in coma, because the mother refused all insulin and dietetic treatment at home. The symptoms of the disease seem to be the same as in adults except that diabetes in early life has a more acute character."

Vascular complications in children are more common than one would expect. ¹⁹ Joslin reports that in contrast to the abolition of coma as a cause of death there is a steady increase of cardio-vascular-renal deaths. Of 42 deaths in 1926, about 50% were due to cardio-vascular-renal, 14% cancer, other causes scattered. "Arteriosclerosis, therefore, has replaced coma as a cause of death in diabetes. So common is arteriosclerosis a factor in diabetes today, that Dr. Morrison was able to demonstrate its presence in 86% of cases of ten years or more duration, studied by xray, and our pathologists found it in every necropsy upon a diabetic, young or old, of five years duration."

In another article,²² Joslin wrote concerning premature arteriosclerosis in children; "I do not believe he has it because he is preordained and predestinated to have it on account of his diabetes, but I believe he has it largely because we doctors give it to him. Low carbohydrate and high fat diet promotes arteriosclerosis; insulin helps because it allows higher carbohydrate and lower fat. Not one of my diabetics now takes less than 50 g. carbohydrate and I am trying to raise their diets gradually to 100 g. carbohydrate. Never overfeed a diabetic and least of all with fat. It is a question whether cholesterol deposits of atheromatosis are premonitions of later calcification. Dog experiments show that when large amounts of cholesterol are fed, the cholesterol content of the blood rises and is accompanied by deposit in tissues. Eggs, olive oil, corn oil are the chief sources of cholesterol. Limit eggs to one a day and discourage excess olive oil and corn oil as found

in salad dressings. Of course it must be remembered that cholesterol is essential; it is found in practically every cell of the body. The blood cholesterol which is a true index of other lipids is now below rather than above the average as found in non diabetics."

The skin²⁰ of an untreated diabetic child is very dry and there is a peculiar canary yellow tint of the skin about the nasolabial fold, under surface of the foot, and palm of the hand possibly due to the pigment carotin. Xanthoma is common, may be localized or generalized, and may disappear with treatment. Lanugo hair was a characteristic sign on the arms, legs and backs of debilitated children undergoing treatment by undernutrition but this has disappeared with improvement in treatment. Under insulin treatment the skin of a diabetic child is of good color, turgor and resists well any invasion of bacteria. Cataracts in children are rare but are rather frequently reported because they are so pathetic and striking a complication. Some cases with cataracts are especially discouraging because the complication did not appear to result from prolonged duration of the disease or from improper treatment which might be corrected in another patient. Height, weight, sexual development have been discussed.

TREATMENT

The ideal³⁹ in treatment is to get the patient on a diet and insulin dosage on which he will live, grow and develop with a normal blood sugar permitting pancreatic rest and possible regeneration of the islands of Langerhans. While the ideal is not often attained, by aspiring to it one can carry them along comfortable, well nourished, and happy to an age of greater cooperation, always with the hope that with improved methods and greater knowledge we will do better.

Without insulin⁸ it was practically impossible to make any severely diabetic child gain weight and hold it. Further, a more marked effect of undernutrition on height was noted than in normal children in whom skeletal growth often proceeds in spite of undernutrition. The readiness with which excessive gains in weight

in diabetics can now be produced by overfeeding plus insulin constitutes one of the dangers of the latter, the obese diabetic being a very poor risk. An initial gain in weight occurs in most children, particularly if underweight, during the first 6-8 weeks of treatment. At this time the tissues are flabby and the face often appears puffy although no demonstrable edema is present. After several weeks the weight curve becomes more or less of a plateau, and little further gain in weight is made for some time. During the period of flattened weight curve, the earlier gains become consolidated. The puffiness disappears from the face and the tissues become firm. Thereafter, the weight curve depends on treatment, particularly the diet. The height of a diabetic child deviates from the normal in direct proportion to the duration of the disease before treatment is started. Taking into consideration family traits, all children tend to reach normal height-weight relationship for their age after faithful dietary and insulin treatment. The fact that the laity usually consider obesity a sign of general well being frequently makes it difficult at first for the physician to have his patient keep the weight at slightly below the normal standard. The fat child is the one who suffers most from hypoglycemic reactions and has the greatest difficulty in keeping urine tests clear for any consecutive period. An analysis of the coma deaths reveals that 80% were more than 20% overweight. Undernutrition is a serious handicap to the diabetic child, but at the same time over nutrition is more dangerous, and experience has proven that if a choice should be made the former is the more desirable. The best relief for obesity lies in adequate exercise which facilitates utilization of sugar and diminishes the tendency to abnormal blood sugar.

Because of precocity¹² of diabetic children, the best cooperation is obtained between the ages of 6 and 12. Under 6 years, they do not recognize responsibility; over 12 years they have the careless adolescent attitude. Education of the diabetic child or of any diabetic is the surest insurance for success in management. Diabetes is probably the only disease in which the patient should know all about

his condition and how to remedy it. The physician's responsibility does not end there. By means of a careful follow up system he should obtain reports at definitely stated intervals to make sure there is no tendency to relax treatment or to neglect urine tests. Some physicians supply the patients with home report sheets for recording diet, body weight, daily urine tests, and insulin dosage.

¹⁸
Joslin says, "We should array them with the best armor that modern hygiene affords. This includes treatment of teeth and tonsils, postural training, protection against small pox, tuberculosis, diphtheria, scarlet fever, typhoid fever, and minor infections, and always adequate sunlight, hours of rest and hours of play. The ten year diabetic¹⁹ should be the finest product of the periodic health examination. The handicap of the diabetic must be offset by the prophylactic treatment of the doctor. No group of individuals is more constantly under the doctor's care, and consequently they constitute what one may call the 'Doctor's Diabetic Trust.' Woe to us physicians if we do not administer that trust in a way to give large returns in dividends of health to our patients."

¹⁵
Fischer developed an apparently satisfactory routine, "The new diabetic child is preferably placed in the ward of a hospital for a period of time so as to study his tolerance and insulin requirement and to educate him in the new mode of life which he will have to follow. After a time, the mother and even the grandmothers of the child are invited to visit the diet kitchen to learn the methods of preparation of the food that the child will eat when he returns to his home. After leaving the hospital, the child keeps a record of the food he eats; after he has proved himself to be accurate, he brings the list of foods eaten on only the day previous to the regular clinic visit. A specimen of each urine voided during the preceding twenty-four hours is brought to the clinic for examination. This eliminates the necessity of routine blood sugar determinations, for more information is gathered from urinalysis of the individual specimens than from a single test of the blood sugar, especially when the morning dose of insulin has

be had to postponed in order to determine in the clinic the blood sugar during fasting. All children over 9 years old give insulin to themselves, but at least two other members of the family must demonstrate their ability to give insulin. The regular visit to the clinic is every 2-3 weeks. This follow-up is very important for it prevents laxness from developing."

The mother³⁰ bears the burden of immediate supervision not only in regard to diet and general physical condition but of almost equal importance that of moral training and discipline. The diabetic child should not be given the privileges of an invalid. He should be held to the same standards of development and behavior as any normal child. It is necessary to develop in him a normal social instinct lest pampering allow him to capitalize on his infirmity even to the point of becoming hypochondriacal. He should not be regarded as a sick child, but should be given opportunity for outlet of his natural restlessness and activity mentally as well as physically. Most diabetic children are unusually eager and anxious to learn and are well equipped mentally, hence teach him, win him over, and then cooperate to help him to lead the life of a normal person.

Many parents³⁵ object to putting apparently healthy children in hospitals for a period of control. A special home for diabetic children would enable them to live a fairly normal outdoor life during the control period and to make friends with other children with the same disease which would be a great comfort and encouragement to them. Competitions might be arranged to help strengthen the children in their endeavor to be faithful to the diet and to the insulin treatments. They would be interested in each other and the fight against the disease would hardly be so exhausting as when they had the feeling of standing quite alone.

The initial period of observation in the hospital includes careful physical examination for foci of infection and careful regulation of diet and insulin with urine analysis and occasional blood sugar determinations. At first the patient is placed upon a sub-maintenance test diet which usually results in disappearance

of sugar from urine. Such a diet would contain 1-2g. protein per kilo body weight and the remainder in carbohydrate and fat with a fatty acid:glucose ratio not over 1.5 . The total calories, at first deficient for maintenance, are increased by addition of carbohydrate and to a much less extent fat and protein, all the time watching the urine carefully for the first appearance of sugar. After determining the tolerance with the test diets, the patient is put upon a maintenance diet with insulin necessary to keep his urine sugar-free. Such a maintenance diet for a child would contain about 2g. protein per kilo body weight for his age with carbohydrate and fat not to exceed fatty acid: glucose ratio of 1.5. Total calories are based on age, the required number is found in such tables as those of Holt. With a satisfactory diet and insulin dosage thus determined, the child leaves the hospital to continue at home; the struggle has just begun.

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It should be remembered that initial treatment should not be inaugurated with sudden alteration or restriction of diet. The most common mistake is usually sudden restriction of carbohydrate. Fat is the one article of diet that should be restricted first irrespective of whether acetone bodies are present or not. Sherrill writes, "The use of rigid diet formulas for determining the required diet of any diabetic patient should be discouraged. It not only restricts individuality, but forces ill-balanced diets upon many diabetics. Imagine one's embarrassment in attempting to give a logical explanation for assigning the same diet to a chubby fat boy and a tall slender girl because they are of the same age and weight. The diet must be arranged to suit the needs of body requirement; fat and carbohydrate being added or restricted as obesity or undernutrition demand. The average child does well on 65 g. protein daily, about 2.5 to 3 g. per kilo. Of course this is average; the protein requirement is in indirect ratio to age of the child. Holt estimated the requirement at about 4 g. per kilo in infancy, 2 to 4 g. in childhood, and 2 g. in adolescence. The diabetic child gains easily in weight but not so easily in height, and in as much as protein is one of the chief essentials for the growth of bony structure, one must make sure of adequate protein allowance in the growing child.

Protein is the ideal food for conserving skeletal musculature; it prevents hunger and helps control obesity. The protein given should allow for a positive nitrogen balance and be sufficient for adequate growth in stature, weight, and development."

Some authors believe that 2-3 g. protein per kilo is more than is necessary. Experiments with diabetic children at full activity between ages 4 and 14 years showed positive nitrogen balance, gain in stature, gain in weight at a normal rate, and normal development when supplied with 0.6 to 1.0 g. protein per kilo provided (a) caloric requirement was fulfilled and (b) the diet was chosen from foods rich in vitamins and containing adequate animal and vegetable sources. "The protein requirement is a function of the ingested calories varying inversely with the caloric intake. The protein requirement bears no relation to the fatty acid:glucose ratio provided it is compatible with a persistent absence of ketosis. The protein requirement varies inversely with the age and is directly proportional to rate of growth." The patients were placed at first on low caloric diets with only 0.6 to 1.0g protein per kilo. When the urine became sugar free and the blood sugar fell to a normal fasting level of 80-120 mg. 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 fatty acid:glucose ratios were between 2.5 and 3.0 with no ketosis. The patients were then studied over periods varying from 4-8 months, their protein intake being kept at a constantly low level. It was thus possible to demonstrate the protein sparing action of the ingestion of fat which had been previously reported by other investigators. Patients were kept in bed while receiving sub maintenance diets and were allowed full activity on maintenance regimes." In forcing the nitrogen metabolism to a minimum it was found that high caloric diets of 80-110 calories per kilo were necessary in the various cases. Bartlett cites other investigators: Dr. Palmer of the Presbyterian Hospital, New York, found protein required was not over 1 g. per kilo; Keith of Rochester, Minnesota found Holt's estimate at least 100 % too high. These investigations are valuable in showing

what can be done, but most clinicians tend to use 2-3g. protein per kilo or about 15% total calories in protein because this added amount guarantees a positive nitrogen balance and also allows an easier choice of a palatable diet that stays with ⁱⁿ the proper limits. Children are usually more easily managed on the lower fat diets permitted by higher protein.

In as much as the child has a small body mass,²³ a high carbohydrate diet tends to create an unstable balance between food intake and insulin dosage. "Carbohydrate³⁰ has a stronger glycosuric effect and creates a higher insulin requirement than the caloric equivalent of any other kind of food. There is no constant insulin dosage for the assimilation of any given quantity of carbohydrate. The ratio between grams of glucose and units of insulin varies widely not only in different patients, but also in the same patient under different conditions. Glycosuria and insulin requirement are governed to a very important degree by the total caloric effect of the diet. Joslin has found it safest to keep the ratio of carbohydrate to fat at about 1:1 ; and his carbohydrate allowance rarely exceeds 100 g. The giving of promiscuous amount of carbohydrate to the diabetic encourages carelessness in diet and very soon all discipline is relaxed with generally poor results. Very soon he is willing to risk more fat and total calories; he grows obese and soon comes to a sad ending. Exaggerated amounts of carbohydrate prevent careful stabilization of the blood sugar. The rapid flooding of the organism brings about prompt glycosuria which is soon followed by hypoglycemia secondary to the high insulin dosage required in an attempt to prevent it. Children require proportionately higher carbohydrate than adults and carbohydrate should be given so long as glycosuria and hyperglycemia can be avoided. In the early stages it is a very simple matter to give large amounts of carbohydrate, 200-250 g. with small amounts of insulin and still maintain sugar freedom, but when one recalls that diabetes is a progressive disease and tolerance soon lowered, it is much better to insist upon lesser amounts of carbohydrate in the diet. Eighty to one hundred grams of carbohydrate

is a very liberal amount and permits comfortable existence. It is adequate for a small amount of starch and cereal, and it is sufficient for a good supply of green vegetables and vitamins.

"Since diabetes³⁰ is a disease of total metabolism rather than a disease of carbohydrate metabolism, the question of fat in the diet must deserve early consideration on account of its high caloric value. The insulin requirement of the body is very greatly increased by the addition of fat to the diet. Increase in adipose tissue on the body demands a much larger insulin supply than does a similar increase in skeletal or bony structure. The increased amount of adipose tissue not only requires extra insulin for the process of food storage and consumption, but the fat cells also consume it at a rapid rate during the process of anabolic and catabolic change." Ladd²³ showed that diabetic children may grow normally on diets which contain only 50% of the total calories considered necessary for the normal child. The criterion for sufficient total calories is an observed increase in growth plus, if necessary, determinations of the nitrogen balance over a sufficient period to establish the fact that it is positive.

Gladys Boyd⁷ reported, "Our interest in the fats contained in the blood was first stimulated by the observation that children on high fat diets, a ratio of 1.5: 1, frequently developed anorexia and ketosis after being on such diets for several months. It appeared, and the earlier cases lent support to the view that developing lipemia might be responsible for the symptoms. Most children on such diets appear to be constantly on the border line of ketosis and insignificant factors produce acetonuria. It would therefore appear that these diets are disadvantageous in the treatment of the youthful diabetic patient whose age and disease both tend readily to produce acidosis from minor disturbances. For these reasons the proportion of carbohydrate in the diet has been increased with beneficial clinical results. The most effective single

factor in the diet in producing lipemia appears to be excessive caloric intake . This applies when the energy intake is sufficient to produce rapid gain in weight or persistence of more than 10 per cent overweight in a child irrespective of the fact that the same number of calories might be fed to another child without producing such an effect. Lipemia is usually present when the patient is 10% or more overweight. Severe acidosis and coma are always accompanied by hyperlipidemia. On the average, blood sugar and blood fat parallel one another in their variation from the normal. Increasing tolerance indicating a more or less constantly normal blood sugar usually results in maintenance of the blood fat at a normal level or a reduction of a preexisting lipemia."

"Before¹⁵ the discovery of insulin and for a period afterward, many authors stressed the importance of keeping diabetic children entirely sugar free. While one attempts to keep them sugar free, one may in so doing defeat the **primary** purpose, namely, the production of normal growth and development. In other words, in attempting to keep the urine entirely sugar free one may be forced to prescribe a low caloric diet which is not compatible with normal gains in weight and height. By increasing the diet and insulin dosage, a child may develop glycosuria some time during the twenty-four hours, yet in spite of glycosuria, gain in height and weight. Thus the presence of an occasional or low grade glycosuria may be compatible with normal growth and development."

The diet should be adequate in substances which enable growth to take place, namely, the vitamins and salts as furnished in fresh vegetables, milk, butter, fresh animal and vegetable proteins. Three glasses of milk daily will supply the calcium content; sufficient fruit and vegetables should be given for bulk to satisfy the appetite. If a child steals food, it is because his diet is inadequate or he has not been instructed properly. The diet should not be sacrificed to the point of undesirability merely to eliminate insulin doses. The child should be shown how to make a game of weighing his food, testing for sugar, sticking to his diet, and watching his sugar tolerance rise. Tell the child the

"why" of the routine so that he may feel his importance and responsibility while also learning how to care for his own needs. Encourage him and explain the harm from neglect.

On account³⁰ of the rapid metabolic changes to which the child diabetic is susceptible, greater responsibility is encountered than in the treatment of adults. Insulin has served to lessen this responsibility and has made it possible for the diabetic child to grow and develop normally. The common latent complications such as neuritis, reinitis, carbuncles and gangrene occur most commonly in diabetics who have been careless with their diet and have failed to keep blood and urine tests clear. Experience with insulin gives assurance that the diabetic child has probably the same expectancy as other children, and with proper prophylaxis in diet and insulin, he should not have in later years the complications to which he is susceptible. Diabetic children sooner or later must be treated with insulin. The quicker it is begun the better the final result because good nutrition is more easily maintained. The musculature of a mildly diabetic child is firm, his complexion clear, and his strength and endurance almost equal to the normal. If he be treated by dietary measures alone for any length of time, he soon loses the good muscular tone, the subcutaneous tissue becomes flabby and pudgy with retained fluid, and his color becomes pale and sallow. Although insulin restores the body weight and strength in such cases, there remains an unmistakable diabetic appearance which has been described as simulating hypothyroid or hypopituitary conditions. With early use of insulin, patients may not only be controlled better from the standpoint of smaller insulin dosage, but better nutrition and management is insured. Patients should take as much insulin as possible without inducing hypoglycemia, rather than use as little insulin as possible to just escape glycosuria. Some claim that hypoglycemia is the best state for pancreatic regeneration.

West,³⁰ in discussion of Sherrill's article, "The problem of keeping the

diabetic child not just alive but also normal is a challenge made possible by insulin. Sherrill's 62 cases show that this ideal can be attained. It is desirable from the standpoint of normal metabolism for the liver to store adequate glycogen; however if the diet, and especially the carbohydrate be in excess and the insulin dosage correspondingly large, excess glycogen will be stored during the periods of insulin activity only to be released as glucose at other periods with consequent hyperglycemia and glycosuria. This occurs typically during the latter periods of the night. The ideal diet would seem to be the lowest one that will provide the actual requirements- protein, mineral, vitamin, and energy value- for normal development and the lowest insulin dosage consistent with control. Otherwise periods of hypoglycemia and glycosuria are almost sure to be present in the same twenty-four hours."

At the onset²³ of diabetes when insulin is not used in therapy, the growth process slows down or ceases altogether. The effect of insulin; (a) Immediate gain in weight (b) Coincident gain in strength and improvement in disposition in spite of the inconvenience of insulin injections. (c) Gain in stature usually follows gain in weight. Some begin to grow tall within a month; in a few , growth does not begin for more than a year. Growth in height does not usually begin until the patient has attained normal weight for height, or in some cases not until the patient has regained the relative body build he had at the onset of diabetes. (d) The gain in stature occurs sooner when the patient is kept sugar free. (e) When there is heavy glycosuria for months there may be failure of growth in stature. This may be simply a matter of caloric loss through urine but growth has been observed to stop in such cases although gain in weight is present. (f) Irregularity of insulin dosage or diet with consequent glycosuria leads to a lowered tolerance and an apparent decrease in efficiency of insulin. Instability of blood sugar causes difficulty in management; the patient passes easily from glycosuria to shock. Stability is regained only after a long period of regular and usually low diet.

"All children¹⁵ now receive insulin. During the past two years five children were treated without it. They did well for a time. Subsequently they lost their tolerance, became sugar free with difficulty on a somewhat lower caloric intake and did not gain weight or grow consistently. At the onset of diabetes one frequently sees this apparent increase in tolerance with a restricted diet and if insulin is being given, it may be discontinued. The sequence in such a case is that for some time, usually from 3-9 months, a child will remain sugar free without insulin; then, generally as the result of a slight infection, glycosuria recurs. It will now be found that the glycosuria is not so readily controlled as previously and that insulin will be required to keep the child sugar free. Most of the children take 2-3 injections daily. Subdividing the dosage of insulin when it seems that there is a loss of tolerance is frequently effective. None of the children gets one injection a day. I feel that insulin is required more than once in twenty-four hours if there is true diabetes, the endogenous insulin not being sufficient to carry the child along with only one therapeutic dose a day."

Toverud³⁵ prescribes insulin three times a day one-half hour before each meal to keep blood sugar at a normal level all day. Insulin usually wears off in four hours. "If only two doses be given, one before breakfast, one before the evening meal; the two carbohydrate meals are taken care of, but in spite of the noon meal being mostly protein and fat, it may nevertheless give rise to high blood sugar as demonstrated in several children. It has been found that after ingesting 100 g. of meat, the blood sugar level rises in normal children to reach a peak in one-half hour, not over 35mg. increase from the fasting level and followed by a rapid drop to or below the fasting level. In diabetic children, hyperglycemia after protein intake amounted to 100 mg. increase, sometimes higher, with the blood sugar level staying high. Hence insulin is needed before the noon day protein-fat meal. Insulin should be given in small frequent doses also because of the low glycogen store in children."

Reactions to insulin are frequent, usually mild and readily controlled by a small amount of carbohydrate orally; often the child recovers without treatment. The first³⁵ and most frequent symptoms are fatigue, paleness, perspiration, feeling of hunger. A small child is cross and cries without being able to tell why. The child is ataxic, talks indistinctly, looks at people in a queer manner, because of diplopia and strabismus. At night he is restless and may awake with a scream. Alarming maniacal attacks and general convulsions may occur. The symptoms are not the same in all children and not always the same in one child. Insulin shock is not always accompanied by hypoglycemia; the blood sugar level at the onset of insulin shock is not always the same in one patient. Toverud has never found it necessary to use intravenous glucose even in a patient, who is unconscious. Open the mouth with a tongue blade and with a pipette put a few drops of 10% or 20% glucose solution on the pharyngeal wall; convulsions cease and consciousness returns in one minute. He regards it as a reflex rather than as instantaneous absorption of glucose. He believes that the sudden rise of blood sugar after glucose intake and even after protein intake also indicates that regulation of blood sugar following food intake is by reflex mechanism. Subcutaneous adrenalin and disodium phosphate are also insulin antidotes.

Muscular exercise³⁵ decreases blood sugar by increasing glycogenolysis thus lowering the glycogen store in the body. If, then, a child whose diet and insulin dose are accurately balanced in the hospital resumes his usual active outdoor life, an insulin shock is apt to occur if the diet is not well controlled. The possibility of such a shock on arrival home should be explained to the parents who should also be told how to treat it and change diet or insulin dose to guard against future attacks. Allen believes that muscles under the stimulus of work make better use of the insulin present or take care of a certain amount of food with less insulin.

At the start,³⁵ the children are often in a poor state of nutrition. With

insulin, an immediate rapid increase in weight, even several kilograms, is followed by a smaller decrease in weight. This is from water retention but such children do now show edema. This is followed by a slow steady increase in weight corresponding to that of normal children provided the diet has been strictly controlled and the insulin needed has been given regularly. If the child eats more than is permitted with consequent glycosuria, he will stop gaining and will lose weight. The question whether carbohydrate tolerance does increase after some years treatment with insulin and dietary control is not readily proven. A patient admitted in coma has a very low carbohydrate tolerance, but the period shortly after recovery from coma shows a relatively high tolerance which is not usually of long standing. After a period, the tolerance reaches a certain level where it stays indefinitely. A boy $2\frac{1}{2}$ years old when his symptoms of diabetes first appeared has had very excellent care by his mother for over three years. He has shown a constant increase in weight and in height and his insulin dose, 14 units daily, has been stationary for the last $2\frac{1}{2}$ years. He had entered the hospital in coma. This points to a larger output of endogenous insulin for as the boy grows he surely needs more insulin which in this case apparently came from his own pancreas. Allen's work on dogs, as already discussed, has shown that hydropic degeneration of the islands of Langerhans is a phenomenon produced by overstrain of the function of the cells by diets in excess of the weakened assimilative power. It is a clinical fact that a constant hyperglycemia will greatly decrease the carbohydrate tolerance. This fact is well illustrated in a boy 9 years old who on the first occasion was admitted comatose to the hospital in a very poor nutritional condition. After he recovered from coma, his weight-height chart soon became normal and on discharge he required only 12 units of insulin daily. In less than a year food indiscretions produced hyperglycemia which his parents could not control by 44 units of insulin daily. In the hospital on the same diet and insulin dosage used outside the hospital, sugar disappeared from the urine, the fasting blood sugar fell to normal and he gained four kilograms. The insulin

requirement fell to 20 units daily. Three months later at home, diet indiscretions led to readmission to the hospital. On dismissal the insulin could not be lowered beyond 52 units daily. Later it was found he had to have 100 units daily. Like all of us, nature resents repeated insults.

In some children³⁵ where the disease has lasted for some time or is of a severe character the blood sugar may be kept normal in the course of the day with three daily doses of insulin half hour before meals, but during the night the blood sugar rises and it does so earlier in the night the more severe the diabetes. The higher blood sugar value throughout the twenty-four hours is the fasting blood sugar in the morning. This night rise is considered a bad prognostic sign. The source of the sugar may be the glycogen stored during the daytime with subsequent glycogenolytic action at night because of lack of insulin. Some investigators consider stored fat as a possible source.

Joslin²² says, "Most diabetic children who have had the disease for several years show glycosuria at some time during the day. Insulin dosage is regulated to precede these periods of glycosuria. To prevent forenoon glycosuria, insulin is given one hour before breakfast or if the urine is not sugar free on rising insulin may be given the night before so that the patient awakens well protected with glycogen stored in the liver."

The labile blood sugar of children is emphasized by Rowe²; "It is difficult to keep the blood sugar as well controlled in the juvenile diabetic as in the adult patient. The therapy must be regulated, however, with the aid of blood sugar determinations, especially when a question of mild insulin reaction arises. In two cases during the last two years, a low renal threshold has demanded a regulation of therapy by rather frequent blood sugar studies and has necessitated the allowance of a slight glycosuria to prevent frequent insulin reactions. Even without such low thresholds I agree with Joslin that it is nearly impossible to keep the average diabetic child sugar free throughout the entire twenty-four hours."

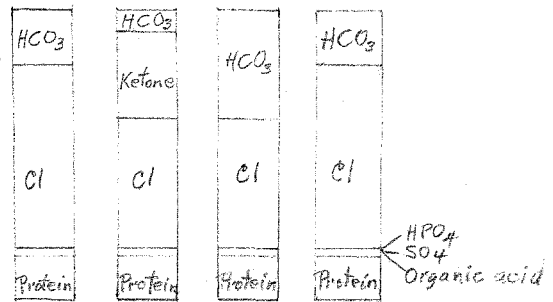
Coma⁹ is still common and 80% of the fatalities are from coma. It often follows or accompanies infection. Often the picture is one of polyphagia, polydipsia, polyuria with constipation and failure to gain if not actual loss of weight, but in babies and in young children failure to thrive and constipation in spite of frequent changes of food may be all that are noted, the degree of emaciation to some extent protecting the infant for a time from more acute symptoms. Those who show acute symptoms of acidosis such as abdominal pain, vomiting, and hyperpnea may die within a week of onset so rapid is the progress of the disease if unchecked. The abdominal pain, rigidity, and coffee ground vomitus are very suggestive of an acute abdominal condition. The degree of drowsiness is not a very good indication of the severity of the coma, so that any degree of stupor even if it be inconstant and the child very bright in the intervals should be regarded as needing immediate attention. Preventive treatment of coma includes, (a) proper treatment of diabetes keeping blood sugar and weight down, (b) adequate removal of foci of infection, (c) careful supervision during infection. Curative treatment of coma consists of ; (a) Reduction of metabolism by putting the patient to bed applying external heat, waiting on him for all his needs. (b) Adequate fluid intake because all comatose patients are dehydrated. Depending upon the age of the patient, he should receive $1\frac{1}{2}$ to 4 liters of fluid every twenty-four hours. During the first twenty-four hours most of it is given parenterally because the patient is unconscious or unable to retain fluid by mouth. Five percent glucose subcutaneously every 4-6 hours or in the more urgent cases 10% glucose intravenously may be given. The Murphy drip should be used when possible. As recovery begins, orange juice or 5% glucose in $\frac{1}{2}$ teaspoonful to table spoonful doses may be given frequently by mouth. (c) Conversion of the patients metabolism to a carbohydrate metabolism. This is relatively easy if the patient be underweight, but it is increasingly difficult with each pound of excess fat. In severe cases 10% glucose is given intravenously every 4-6 hours. The pulse should be watched and at any weakening or increased

regularity the injection should be stopped at once. The injection must be slow and the total amount not exceed 10 c.c. per pound body weight. Normal saline subcutaneously is given immediately afterwards. The fluid injections must be repeated every 4-6 hours until the patient is able to take and retain fluids by mouth. It is seldom if ever necessary to repeat the intravenous injection. In less urgent cases, all the fluid may be given subcutaneously and by rectum and the intravenous route left untouched. Oral administration of fluids replaces the other methods used as soon as possible. (d) Administration of chlorides to make up for the depletion usually present. It prevents the patient from going into alkalosis from acidosis.

It is easy to explain the need for chloride administration by the use of charts.

Blood Acids in Terms of N/10

In column 1 is represented the normal acid portion of the blood. The base occupies a similar column of equal height but does not concern us much here. It will be noted that chlorides and bicarbonates in terms of deci normal acid occupy the large proportion of the acid portion of the blood. Column 2 represents what happens in



diabetic acidosis; the chlorides and bicarbonate are both decreased in amount and ketone bodies occupy a portion of the space which they would normally occupy.

Now when large quantities of glucose and insulin are given, the blood changes are produced such as those in column 3. It will be seen that ketones have gone, the bicarbonate has increased not only to occupy their place but that of the lowered chlorides as well, and alkalosis has been produced. If, however, sodium chloride be given with the glucose, which may be made up in normal saline, the chlorides will have increased as the ketones decreased, and the rather labile bicarbonate will have been kept within its normal limits. One saline administration is adequate in most cases but when vomiting has been prolonged or is persistent, more should be given. Should the timely administration of saline be neglected and the development of alkalosis be suspected from the deepening coma or prolonged

respirations, 2-4 g. of ammonium chloride should be given by the stomach tube.

(e) Administration of insulin as soon as the diabetic coma is diagnosed. In severe coma 40-50 units with glucose intravenously, 2 units to 1 g. glucose, are given. In less severe cases 1 unit of insulin is given subcutaneously for each gram of glucose subcutaneously. After the patient is able to take adequate carbohydrate and fluid by mouth, small doses of insulin, 10-15 units, are given every four hours till urine is sugar free. It is not advisable to keep the patient aglycosuric until he is fully conscious because of the danger of hypoglycemia. (f) Attention to the gastro intestinal tract. The stomach is usually dilated, sometimes extremely so, and if coma has been present long, coffee ground material is present. In cases where vomiting and distension persist in spite of general treatment of the coma, a careful lavage with sodium bicarbonate 5 g. to a pint of water is often distinctly beneficial. There is no need to employ it as routine for all cases. Constipation is usually marked and progress toward cure of the coma is often checked by the presence of retained fecal matter. High colonic irrigations are to be preferred to cathartics and they should be repeated every four hours until relief is obtained. Use normal salt or sodium bicarbonate 5 g. to a pint of water for the colonic irritations. After coma has been overcome an easily digested diet should be provided. (g) Guard against circulatory failure. The injection of fluids should be slow and not over 10 c.c. per pound body weight as described above. In severe cases the heart should be stimulated every two hours with alternate doses of digitalin and caffeine sodio benzoate.

The very latest idea on treatment of coma with insulin is to more closely simulate nature by giving small doses, 5-10 units, every 15-30 minutes testing for sugar in the urine before each dose of insulin. The administration of small doses of sodium bicarbonate seems to be gaining some favor but of course this doesn't mean neglect in adequate insulin dosage.

25

The use of insulin for the control of diabetes in infants meets with difficulty in the way of arriving at a satisfactory dosage. Great variations will occur in the

blood sugar and glycosuria of an infant in twenty-four hours. Wood attributes this sudden variation to the lability of the metabolic processes. The size of the individual is no doubt also a factor. Some permit a small amount of sugar to be present in the urine as an alternative to slight hypoglycemic reactions. The latter are represented by symptoms much the same as in the adult but must be detected by objective signs, The most manifest are hunger, weakness as evidenced by limpness and dizziness, pallor, cold sweats, convulsions and coma. These symptoms are so evident that the mother is able to detect them at the onset of a reaction. Orange juice is the usual form of carbohydrate given; it may be given per rectal tube or nasal tube, or orally if a few minims of adrenalin have first been used to elevate the blood sugar sufficiently to restore consciousness so that the patient may swallow. Intravenous glucose may be used if necessary.

²²
Aggravation of the diabetes by infection must be met with skillful adjustment of diet and insulin. The total caloric intake is reduced by reducing fats much and protein slightly. The amount of carbohydrate is maintained or even slightly increased and the insulin dosage is adjusted by the hour instead of by the day. It is usually necessary to increase insulin frequently both in total number of units and in the number of daily injections until the infection has subsided and the lost tolerance has begun to return. Ordinary diseases and operations are withstood very well; appendicitis is the most dangerous surgical problem because it so closely resembles diabetic coma and may be associated with it. Nausea, vomiting, pain in abdomen and leucocytosis are common to both diabetic coma and appendicitis. If in doubt, the operation should be done because appendicitis may occur with diabetic coma.

³⁵
Blood sugar regulation is so sensitive to a slight infection that a rise in the fasting blood sugar curve often precedes a rise in body temperature. The decrease in tolerance often persists after the infection is gone. As a rule the child will tolerate higher doses of insulin when an infection is present. Even if the food intake be lowered considerably, the patient may sometimes take double the

usual daily insulin dosage without showing symptoms of insulin shock. If such a change in the insulin dosage be made quickly and under close control of the blood sugar, the infection usually soon subsides and the child's carbohydrate tolerance is quickly regained. Such close observation is often not possible, hence the rather high mortality or greatly lessened carbohydrate tolerance which results. The increased metabolic rate of infection does not afford adequate explanation for increased need for insulin because in some cases there is no increase in metabolic rate although the infection has the same bad effect upon sugar tolerance. There is no proof of toxic action; a toxin usually has a specific effect. The factor of acidosis present during most infection in childhood may play a role. It is a fact that the presence of acidosis greatly increases the insulin requirement, reason unknown. After all, prophylaxis is the best treatment of infection; foci such as teeth, tonsils, adenoids, kidneys should not be permitted to harbor infection.

The disease seems to be progressive in some cases even if insulin is administered. This appears to be due mostly to poor control of the diet and to recurrence of infection particularly in the upper respiratory tract. The disease in many cases will become stationary and the patient may even show an increase in carbohydrate tolerance if the diet is well controlled and the infections reduced to a minimum. This possibility must never be forgotten when one is asked by parents and relatives about the outlook for a diabetic child and particularly if there is doubt whether insulin treatment ought to be started. Joslin and other authorities have found that it is best to keep most children upon small doses of insulin even though they can be made sugar free with dieting alone. Diabetes in children should always be regarded as potentially severe for it is not rare for a child to suddenly show a much lower sugar tolerance. If the parents and child already understand insulin therapy, they are better able to meet these sudden changes until a physician may be called.

Ultra violet rays, yeast vitamin B₁ and irradiated yeast have been used in an attempt to find a therapeutic agent as valuable as insulin but which did not have its disadvantages, namely; transiency, danger of overdosage, difficulties in mode of

administration. Three diabetic children were given ultra violet rays, two patients took irradiated yeast; **four** patients took yeast. The relation of dextrose consumed to insulin dosage, called the dextrose-insulin quotient, was used as an indication of sugar tolerance. In all the patients the dextrose-insulin quotient remained practically constant during the pre-experimental two months, the time of experimentation, and the two months following the experiment. It was concluded that ultraviolet rays, yeast vitamin B, and irradiated yeast when administered over a period of four to seven weeks, fail to produce any significant improvement in the sugar tolerance of children with diabetes.

Summer camps are being arranged for diabetic children in an attempt to give them the joys normal children have and to improve their general health. Seven patients¹⁴ ranging in age from 8-15 years were taken from the outpatient department of Mount Sinai Hospital, New York, and kept six weeks on a farm seventy miles from New York City. An experienced dietician was in immediate charge but a report was mailed to the physician every second or third day. He regulated diet and insulin dosage except in emergency when the dietician reduced insulin immediately in case of obvious overdosage. Several times the physician was phoned because of mild insulin shocks which were easily controlled by small lumps of sugar or slices of orange; no accidents happened that required the physician's attendance.

On arrival, all children were started upon the diets which they had been using at home. Because of their increased activity, their food soon had to be increased in bulk to satisfy their appetites. Each child weighed his own food, did a qualitative analysis of his own urine four times a day, and administered insulin to himself. The dietician corrected errors in technique and required each child to keep his own insulin outfit and to sterilize it before each injection. Most of the children gained in weight, height, and tolerance for sugar. One patient gained six pounds in the six weeks and another whose disease had been of five years' duration had her insulin dosage reduced 75 to 55 units per day and her 11 P.M. injection omitted. She had been on strict observation at several times before going to camp, hence her improvement was real and not due merely to a stricter regimen. She was

able to continue her diet and reduced insulin dosage after her return from camp. Her diet has not been changed in the past year. The turgor and well being were improved in all the children. As a result of their six weeks outing, the children understood the disease better, were more capable of taking care of themselves and felt more that the joys of normal children were their joys too. In addition, the mothers who had been bearing the burden of watching out for these children were given a well deserved vacation.

A summer camp³⁷ on a somewhat larger scale has been conducted in Michigan. With the help of several friends and the Detroit Community Fund, the Grace Hospital Diabetic Clinic has been able to give its children for the past four years a two week's vacation in the country each August. From a very small beginning it has grown each year until in 1929 thirty-one children were accommodated. The food was prepared and cooked by two cooks who were diabetic patients. The children were under the direct care of a special nurse who had been trained in the duties of the camp and was well versed in the treatment of acidosis, hypoglycemia, and other special complications of diabetes. There was a play supervisor for boys and one for girls. A dietician was in direct charge but a physician visited the camp on alternate days to make necessary changes in treatment, diet or insulin dosage, and to take blood sugars when required. Each day was filled with duties, play, entertainment, regular meals with no eating between times. The nurse inspected each child daily for cleanliness, bruises, or injuries; gave the insulin, recorded the temperature and pulse; and supervised the examinations of the urine. Children who were not sugar free or who were having hypoglycemic reaction were kept under close watch for twenty-four hours. Every child became sugar free in camp; many had reductions in their insulin dosage, and others were able to take larger diets. It seemed that the increased exercise in the fresh air markedly increased the carbohydrate tolerance. Many children had been on monotonous diets and were pleasantly surprised with foods they had not tasted before. For a short period each day, the older ones were given instruction in dietetics, that they might be able to better substitute foods when they returned home. The interest manifested

in these talks was very amusing, especially when some child learned that he could have a certain amount of bread and milk in place of another food which had become monotonous.

This camp provided a vacation for children and parents that would not have been possible otherwise. The children were enabled to associate with others without the pity which is usually bestowed upon them. This association with other children seemed to develop their mental faculties; it taught them to do things other children were doing.

Rowe² suggests three reasons for poor results in treatment: (a) insufficient education of parents in regard to diet, insulin regulation, and the control of complications, (b) poor cooperation of the child especially in the eating of extra food, and (c) most important of all, the lack of frequent follow up of the patient by the physician who has assumed the responsibility of the protection and treatment of the juvenile diabetic. Injury³⁰ from improper diet and breaking of diet is much more quickly demonstrated in children than in adults. A period of hyperglycemia and glycosuria throws a strain upon the pancreas which often results in lowered sugar tolerance. The following case¹¹ shows what may happen. During the thirty-four months after first admission to the hospital in coma a colored girl, age 11 years, was readmitted twelve times in severe acidosis or coma, spending 549 days out of 1131 days in the ward. Neglect of proper management at home had allowed repeated dietary excesses. The child responded with relative ease to treatment each time, but successive insults resulted in progressive lowering of sugar tolerance and death after a Thanksgiving Day dietary excess when the patient was not brought to the hospital for treatment. Such gross negligence on the part of the parents is nothing short of criminal.

Because² insulin therapy has so greatly changed the prognosis of diabetes, it is of great importance to carefully investigate deaths of diabetics. In a recent study of seventeen deaths it was found that two died from disease not related to

diabetes, and their glycosuria was carefully controlled by insulin therapy. Most of the remainder died in coma, a preventable accident. The mother of one patient did not use as much insulin as necessary because of the "torture" of injections. The child died in one month. Some parents were too lazy to give their children the proper diet and took them to chiropractors. Parents must appreciate their moral responsibility to the child. The decision as to whether or not the treatment is to be continued or is worth while can be made with justice only by the child after it has come at least into adolescence or better into adult life.

The pessimism of some physicians caused some of the deaths. One physician wrote to Mayo clinic: "Children who were afflicted with diabetes never lasted long under the old methods of treatment and it seems that they do not last much longer under insulin treatment."

Another physician wrote: "A hypo of morphia gave temporary relief. They gave her insulin after this but she died the next day. It seems to me that the disease goes on in spite of insulin and every other measure." Another case had abdominal pain and vomiting which led to a diagnosis of appendicitis till too late to save the child who when brought in had been in coma twenty-eight hours. In another instance defective Benedict's reagent was to blame for the death. Poor supervision of patients after they leave the doctor's immediate care is too often to blame. The handicap of the diabetic must be offset by the prophylactic treatment of periodic health examination. No group of individuals is more constantly under a doctor's care and consequently they constitute what one may call the Doctor's Diabetic Trust.

UNUSUAL CASES

It would indeed be gratifying to clinicians as well as to patients and relatives if there could be many more reactions to treatment such as the following case.⁶ A girl, age 11 years, was admitted to the clinic in coma, Sept. 12, 1926. Her symptoms had begun two weeks before entry. The patient was in a state typical of diabetic coma, and she was given 240 units of insulin in the first

twenty-five hours. She was discharged Sept. 30, 1926 on a restricted diet and 53 units of insulin daily. In October only 32 units were necessary. In December her urine was sugar free, fasting blood sugar 110 mg., insulin only 26 units. She continued to have slight insulin reactions until Jan. 8, 1927 when she was using only 2 units daily. Insulin was then discontinued and on March 8, 1927 the fasting blood sugar was 110. mg. without insulin. Insulin was necessary for one week in Sept. 1927 following a break in diet but since then none has been used. July 26, 1928 the fasting blood sugar was 120 mg. The patient has been very active on her school volley ball and basket ball teams and she ranks at the head of her class in high school. Research workers have shown that insulin given early to depancreatized dogs halts hydropic degeneration in the cells of the islands of Langerhans. In this case the disease was apparently of such short duration when coma occurred that probably very little destruction had taken place in the islands of Langerhans, and a large percentage of their cells were given an opportunity to regenerate.

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Other cases are equally puzzling but a great deal less encouraging. A girl, 2 years and 11 months old, was brought to the doctor because for the previous six weeks she had had polyuria, enuresis, unusual hunger and thirst, and was losing weight. Glycosuria and acetonuria with a blood sugar of 160 mg. with the above history seemed sufficient for the diagnosis. On a diet containing 937 calories with 67C, 55P, 61F it was found advisable to give insulin because her tolerance was only 70G. Her father, a chemist, made daily tests on the usual five specimens of urine. With the most careful management, the doctor has been unable to keep the twenty-four hour urine sugar free for more than a few days at a time without insulin reactions, often quite severe. Several times she awakened her parents at night by suddenly screaming. One time at 2 A.M. she was apparently terrified and in a cold perspiration, complaining of hurting in abdomen. A few minutes later she was mumbling incoherently. The doctor was called and he arrived twenty minutes after the onset. She could then be aroused with difficulty, her skin was pale and moist, pupils large, eyeballs moving slowly, respirations irregular, pulse

weak and temperature subnormal. Supper to bedtime specimens of urine contained sugar. The reaction, however, was so typical that the parents had tried to give her Karo corn syrup by mouth but without success. Later her jaws became rigid. Glucose solution per bowel resulted in such rapid improvement that in $1\frac{1}{2}$ hours she talked and played, finally fell asleep and in the morning appeared as usual and remembered nothing of her night's experience. At no time, except twice when she was otherwise ill, has she received more than 16 units daily. Reduction of insulin results in a higher glycosuria and loss of weight. Shifting the diet results in the appearance of acid bodies in the urine when the ratio of fatty acid to glucose goes above 1:1. Now at the age of 5 years, 4 months, the patient is uniformly developed, only a little under normal weight and height for her age, good color, healthy in appearance and she plays in a normal way.

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Another patient was unusual because he was colored, very young, peculiar in reaction to ultra violet light, and also because he recovered from beginning gangrene and is doing well at home under diet and insulin management by his colored mother. The onset of symptoms followed a bruise to his chin which became infected. Several furuncles appeared on his body and an injury to the little finger of his left hand gradually became blackish blue and remained so till admission to the hospital. He had been showing typical symptoms, polyuria, polydipsia, polyphagia, for two weeks. At entry he complained of pain in the abdomen and could not be completely aroused. After the patient had been in the hospital for one month, ultra violet light was used as an adjunct to his treatment. At this time his diet had been unchanged for two weeks and the amount of insulin taken had been unchanged for ten days. He was given ultra violet light for five minutes at a distance of thirty inches. Two hours later the patient suffered the severest form of insulin shock, with unconsciousness, convulsions, cold hands and feet and very shallow inspirations. After introduction of orange juice and glucose by gavage, the patient regained consciousness in twenty minutes. This shock

was followed by three or four hours of wild delirium and hallucinations. Lumbar puncture gave the greatest relief. Further ultra violet light treatments were given, but no insulin shocks resulted; it is very interesting that during the following month, the patient was able to metabolize 1200 calories per day for fourteen days with no insulin whatsoever. Infection of the nose and throat intervened at this time and insulin was again necessary three times a day. After a year in the hospital the boy presented good muscular tone, good color, negative tuberculin test, good nutrition and seemed in every way much above the average colored child in general development.

Feinblatt¹³ reported the case of a Jewish girl, aged 9 years, who was admitted in coma with Kussmaul breathing and acetone odor to her breath. She had been in good health till three weeks prior to admission when she began to have increased frequency and volume of urination, pronounced thirst, itching of the skin and progressive loss of weight. Later she complained of slight disturbance of vision and headache, and two days before entering the hospital there was projectile vomiting not dependent upon the taking of food. In the hospital the findings were: only an insignificant ketonuria in spite of extreme acidosis (CO_2 combining power 14.3% by volume); the presence of a large amount of acetone in the spinal fluid notwithstanding its absence from the blood; failure of enormous doses of insulin (110 units in 12 hours) to influence the blood sugar which was 333 mg. when she entered the hospital and 333 mg. when she died twenty-one hours later.

Revillet in 1914 reported a fatal case in coma with no acetone in the urine. Rosenbloom in 1915 reported three patients whose urine contained no acetone or diacetic acid and contained a normal amount of ammonia nitrogen. Starr and Fitz in 1924 reported a study on 114 samples of urine from eighteen diabetic patients as to their content of acetone bodies and undetermined organic acids. They found that in about 10% of instances organic acids other than the acetone bodies were present in considerably higher than normal concentration. They believe that in certain cases of diabetic acidosis organic acids other than the

ketones are encountered and may play a part in the production of symptoms.

ISOLATION OF TAIL OF PANCREAS IN A DIABETIC CHILD

³⁴
This work was stimulated by the previous reports of Mansfield who first observed an increase of tolerance in dogs following ligation of the body of the pancreas. Hypertrophy of the islets, after obliteration of the duct was first demonstrated experimentally, by Bensley and by Herxheimer. A similar hypertrophy has since been observed in human material at autopsy. De Takats reported additional evidence from his dog experiments which showed hypertrophy and function of the islet tissue in the tail of the pancreas after separation of the tail from the body of the gland. An increased tolerance for sugar has been demonstrated in these dogs with dextrose test meals and by means of intravenous injections of glucose at timed rates. An injection of epinephrine produced in them a less marked hyperglycemia than normal or a paradoxical hypoglycemia.

This experimental and pathological experience naturally raised the question whether hypertrophy of the islets and increased islet function could be brought about in a case of diabetes. Although it is conspicuous in diabetes that the severity of the disease in no way parallels the degree of morphologic alteration of islet tissue, it was considered possible that new formed islet tissue might be less subject to inhibitive influences, particularly those of nervous origin, than the original tissue and therefore the contemplated operation offered some hope. A patient was selected in whom the diabetes was considered to be beyond the stage when improvement from medical management could be anticipated.

Diabetes is a disease that varies greatly in severity, not only from one patient to another, but in the same patient. This is particularly true of the disease in adults. In children, marked fluctuations in severity occur early in the course of the disease although after the first three or four years improvement is decidedly uncommon. Therefore any conclusions as to the value of any therapeutic procedure that may be undertaken in diabetes are extremely hazardous with adult patients or with early diabetes in childhood. This boy 13 years old, was selected

because; (a) he was a child with diabetes of severity; (b) the duration of the diabetes was more than seven years (c) the patient had been under personal supervision five years and nine months during which time the control of the diet and insulin administration had been reasonably precise; (d) the tolerance had never shown any sign of spontaneous improvement,—the disease had reached a degree of moderate severity within two years and eight months and had been nearly stationary thereafter; (e) very scrupulous and exact control had been maintained, for the preceding eighteen months with no change in diet. During those months the smallest daily dose of insulin that would prevent glycosuria was 40 units, frequently larger doses were required.

The situation was carefully explained to all concerned and the decision was reached to put the matter to a trial. Thorough physical examination showed that the boy was in good condition. The pancreas was divided close to the midline by electro-surgical cautery, isolating about 3 cm. of the tail in which the circulation seemed to be well preserved. The severed portion was wrapped in omentum. The rationale of this operation was to produce an atrophy of the acinose structures and to create conditions such as are produced by experimental duct ligation and by pathological processes that involve or compress the ducts. In similar experiments upon dogs, there had been noted a definite change in histologic appearance and in sugar tolerance after a period of three to four months. In this diabetic child an increase in sugar tolerance measured by the decrease of insulin requirement under constant diet, was first noted four months after the operation. It was found possible to change from 40 units to 25 units daily on a constant diet that was the same as that used before operation. Evaluation of results of operation: (a) "Years of close study will be necessary to determine the end result. (b) Because of the abnormally short splenic portion of the pancreas in this case, only a small part of the tail could be isolated. It is possible that if more gland had been isolated a more marked result would have been obtained. (c) Notwithstanding the small size of the portion isolated and despite serious post operative

complications, the patients diabetes had not become any worse and now appears to be somewhat less severe than it was before our operative intervention. Summary: The operation described here was designed to promote hypertrophy of the islet tissue of the pancreas and thereby increase the insulin output from the gland. This operation was performed on a child with severe diabetes with results that are encouraging."

PROGNOSIS and CONCLUSIONS

Diabetes in children should always be regarded as a potentially severe disease demanding close supervision. At the same time, the outlook is not only good but much better than that of the adult since proper treatment leads to improvement in carbohydrate tolerance. Generally speaking⁸, the younger the child the more acute the disease and the more difficult it is to establish control. On the other hand, improvement in tolerance and pathological evidence of regeneration are more marked the younger the child, provided control can be established and maintained. Cases of hereditary or familial nature often appear milder but the earlier diagnosis usually made in these cases may be responsible for their apparent mildness. Diabetes in children is a rapidly progressive disease which may not only be arrested in its course but made less severe under adequate treatment with diet and insulin. The criterion of successful treatment consists in absence of glycosuria and maintenance of normal blood sugar for the greater part of the time. Fluctuations in tolerance are frequent and gains may only be retained by fidelity to treatment.

The depression of tolerance⁸ from infection is only transitory if the patient be properly handled by dietary restriction and increased insulin. Influenzal infections seem worst. Obesity in glycosuria cases increases the need of insulin and should acidosis or coma develop it makes recovery far more doubtful. The incidence of diabetic coma has not declined but a material decrease in mortality due first to insulin and secondly to earlier recognition and treatment has occurred.

There is as yet no sound basis for predicting even roughly just how a child's diabetes will be a year or two years hence. Rabinowitch attempted to determine

statistically whether in juvenile diabetes the blood cholesterol is related to and can afford an index of progress. He found that children with glycosuria, those in whom diabetes was not well controlled, tend to have a high cholesterol content in the blood. He believes that the cholesterol content of the blood plasma is an index of progress.

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Joslin is particularly enthusiastic about the better outlook for diabetic children. "Every diabetic I see whose onset is above age 67 years lowers the average duration of all my cases. Therefore I welcome the young diabetic and the younger the better. This last year the mortality for the 1,205 cases I saw and traced was 3.5 % but for the 235 children of whom I know the condition of all but two, was 1.3% .*****But one thing I know, whereas my diabetic children died, now they live. The duration of life of the average diabetic child in my group has advanced ~~one~~ year these last twelve months. *****As the duration of diabetes lengthens, its symptoms lessen and fade away." Although it is not advisable to predict for any one diabetic child, Joslin's statistics offer much hope which spurs one on to an effort to keep as many children as possible in the satisfactory group already forming the large majority of diabetic children.

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H.L. Wilder of Texas lacks confidence in the ability of his patients and their parents. He believes diabetes in children is incurable not because the cure is unavailable but because of poor management at home. This is a challenge not only to patients and to parents but also to physicians who should be particularly painstaking in adequately instructing and checking up on their diabetics. Joslin ²² reminds us that it is the uneducated, untrained, uncared for child in a family with limited resources who is lost. Every diabetic patient needs someone, a relative or a friend, a "buddy" who will appraise his health each day and when in doubt report him to his family physician.

The hope that in the future diabetes may be cured instead of just controlled is not unfounded because (a) pathological evidence as found from post mortem examination reveals little anatomic change, (b) experimental evidence shows regeneration

of islands of Langerhans, and (c) clinical evidence indicates increased sugar tolerance under good management.

With modern treatment a diabetic child is expected to be normal in development and growth. In as much as he is apt to be precocious³⁰ and his dietary and physical routines are so closely supervised, there is every reason for his being a truly precocious child. The number of diabetic children on the honor rolls of their schools is evidence that this should be expected.

Information¹⁰ obtained from a study of physiologic progress of diabetic children under modern regimen should be applicable to problems concerning the nutrition and development of non diabetic children. When the normal person is studied, his many compensatory mechanisms will often mask a response which would be obvious if his margin of metabolic balance were reduced to the minimum as is the case in children with diabetes. Children suffering with diabetes, if untreated, react rapidly to adverse conditions by diminution of growth. A regimen which will result in normal development in these children should be even more effective if applied to the non diabetic child.

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