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Glycogen Storage Disease and Galactosemia

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I. CLINICAL AND METABOLIC STUDIES OF VON GIERKE'S GLYCOGEN STORAGE DISEASE AND OF GALACTOSEMIA

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Von Gierke's glycogen storage disease and galactosemia are rare congenital disorders involving fundamental disturbances in carbohydrate metabolism. Although Wagner[1] described a clinical case strongly suggestive of glycogen storage disease of the liver in 1921, von Gierke[2] was the first to describe the pathology and to recognize the nature of the condition. Intolerance to galactose was first reported by Von Reuss[3] in 1908. The first case report of the latter disorder recorded in the American literature was that by Mason and Turner[4] in 1935. Twenty-seven cases exclusive of our own have been reported to date, the majority during the past 7 years.

Our interest in these diseases was stimulated by success in the treatment of certain hypoglycemic states with adrenocorticotropic hormone[5]. Both diseases under discussion are known to have low levels of blood glucose in the fasting state. The present report deals mainly with this aspect of the problem, although several other interesting observations have been made during the investigation.

Von Gierke's disease is characterized by the abnormal tendency to store excessive amounts of glycogen within the cells of various parenchymatous organs, particularly those of the liver, heart, and kidneys, and to a lesser extent of the skin and skeletal muscle. Mason and Anderson[6] have classified the disorder into four basic types. The types have in common certain features, such as onset in early life, and hepatomegaly due to excessive carbohydrate deposition in the liver. The clinical types are classified as follows:

1. The classical von Gierke type, characterized by (a) marked hepatomegaly, (b) fasting hypoglycemia and acetonuria, (c) subnormal glycogenolytic response to injection of epinephrine, (d) glucose tolerance test showing a hyperglycemic curve of longer than normal duration and, in contrast, (e) normal galactose and fructose tolerance tests. Histological and chemical examinations of liver sections for glycogen demonstrate its presence in great excess. Lipemia and an excess of fat in the liver may or may not be present. The primary defect appears to be in the enzyme system or systems responsible for glycogenolysis.

2. A hepatic type, showing (a) cirrhosis as well as excessive storage of glycogen in the enlarged liver, (b) absence of fasting hypoglycemia and ketonuria, (c) liver function tests indicative of hepatic damage, (d) less marked impairment of the glycogenolytic response to epinephrine than that characterizing the classical von Gierke type, (e) splenomegaly and, at times, (f) ascites.

3. A cardiomegalic form, in which glycogen storage is predominantly in the cardiac and striated muscles, although the liver and other viscera are also involved. It is characterized by (a) cardiac hypertrophy (globular heart) with early failure, (b) electrocardiographic abnormalities, such as left axis deviation, inversion of the T wave and widening of the QRS complex, (c) no fasting hypoglycemia or ketosis, (d) normal glucose tolerance test and (e) normal response to injection of epinephrine.

4. A galactosemic type, characterized by (a) hepatomegaly due to excessive storage of glycogen, which is more pronounced when a large amount of milk is regularly consumed but is ameliorated by omission of milk (lactose) entirely from the diet, (b) abnormal galactose tolerance test, (c) bilateral cataracts, thought to be due to galactose ingestion, and (d) mental retardation.

The basic cause of essential glycogenosis is not known, but it is tentatively considered to be a genetic aberration in the enzyme systems having to do with glycogenolysis and in some cases with glycogenesis as well. In a study of three

cases of the classical von Gierke type, Cori found glucose-6 phosphatase to be diminished or absent from the liver. In the liver of one of Anderson's patients with the second type described above, Cori and associates demonstrated the presence of glycogen having an abnormal molecular structure that behaved more like starch than glycogen but was definitely not starch.

Representative cases will be reviewed.

A. Glycogen storage disease -- von Gierke type.

., a 20 month old female was referred to us for special studies by Dr. John Bigler of Chicago. A diagnosis of the von Gierke type of glycogenosis was made at the Children's Memorial Hospital by typical laboratory and clinical findings, including biopsy of the liver[7]. The family became concerned when she had several convulsive seizures in the early morning hours. Her abdomen had been large since birth, and her physical growth had been slow. On examination, she was observed as a small (8 kg) child with a doll-like face. The abdomen was large, and the liver was very large and firm, extending nearly to the umbilicus. The fasting blood sugar was very low, but no convulsions were observed. Blood glucose values from 18 to 48 mg % were found during the fasting state. Morning acetonuria was repeatedly observed.

A metabolic study was planned to evaluate the metabolic and clinical effects of ACTH. This study has been reported in detail elsewhere[8]. When the usual dosages of corticotropin for age were given, only a slight rise in the fasting blood sugar was observed. In previous studies on children with non-Addisonian hypoglycemosis[9], this amount of hormone (10 mg. q 6 h) produced a consistant rise of blood sugar to high normal levels. We, therefore, administered increasing dosages to J.J. until the desired response was obtained. It was not until 40 mg of ACTH q 6 h was given that the fasting blood sugar rose to a maximal level of 74 mg %. That the adrenal cortex was undergoing stimulation by the smaller dosages of ACTH seems evident by other metabolic changes that were observed. The usual retention of Na, Cl and water, as well as increased amounts of urinary potassium, nitrogen, and 17-ketosteroids appeared immediately at the lower dosage levels. The serum potassium fell from 5.03 to 3.22 meq/L. Although the levels of blood eosinophiles was low preceeding the hormone therapy, and remained low during ACTH administration, it rose to high levels at the end of the therapeutic trial. The previously mentioned acetonuria nearly disappeared during treatment, and reappeared in the post period. Forty-eight hours after ACTH was discontinued, the blood sugar values returned to hypoglycemic levels.

There was a notable clinical response to the hormone administration. The appetite, which had previously been poor, became ravenous. She appeared more cheerful and cooperative. The liver size, however, did not change during the short period of therapy.

After an interval of 10 days, the hormone was again administered in a dosage of 10 mg. every six hours for four days to determine whether the previously noted freedom from hypoglycemia and clinical improvement would return. Approximately the same response was obtained. The fasting blood glucose levels rose as high as 62 mg. %.

_. _. was an 18-year-old male who was studied by our laboratory while he was a patient on the Medical Service. Our grateful acknowledgement to Dr. C. J. Watson and his staff is made for their cooperation and help in this study.

Hepatomegaly was first noted in the case of this patient during the neonatal period. Convulsive seizures first occurred at 7 days of age, and recurred nearly daily until he was 5 years old. These usually occurred in the early morning hours, were clonic in type, and lasted from 30 minutes to as long as seven hours. He awakened feeling very hungry and always perspired profusely.

Because of daily vomiting in the first year of life, he was studied at the Mayo Clinic. During a trial on a high-fat diet, he became jaundiced and lost a large amount of weight. His growth was slow, and he always appeared short and had a very protuberant abdomen. During a period of hospitalization for tonsillectomy at age 8 years, fasting hypoglycemia was discovered. Because he still had fairly frequent morning convulsions, he was given dilantin, but the seizures continued.

The onset of pubertal changes began late. At age 16, he was 5 feet 1 inch tall, had a slight build, and the abdomen was very prominent. During this year, however, maturation began, and was accompanied by a marked increase in height, a relative decrease in the size of his abdomen, and a decreasing frequency of the convulsions.

Six months before admission here, a thorough investigation of his status was under the direction of Dr. Frank J. Hirschboeck at Duluth, who kindly referred him for additional studies. Unresponsiveness of the blood glucose to epinephrine was noted. A severe convulsion occurred during an insulin tolerance test. A diagnosis of glycogen storage disease was again made. He was given mebaral and instructions to remain on a diet high in protein. His response to this was good, and no further seizures occurred. He was admitted to the University Hospital for further metabolic studies, as well as for an evaluation of his "emotional instability" in April, 1952.

Our physical examination showed him to be 5 ft. 9 inches tall and to weigh 143 pounds. The body build was not remarkable except for slight prominence of the abdomen. Mild facial acne was present, and the muscle and genital development was mature. Body hair was normal in amount and masculine in distribution including beard. His face appeared puffy, but no pitting edema was present. A soft systolic murmur in the pulmonary area was heard. No significant cardiac abnormalities were found. There were no dilated abdominal veins. The liver was markedly enlarged and moderately firm. The enlargement extended 3 to 4 cm. below the costal margins in either mid-clavicular line. On the left, a pointed portion of the liver simulated a palpable spleen. Evaluation by members of the Department of Psychiatry showed his intelligence to be normal (IQ,105 - Wechsler-Bellevue). Except for a mild degree of reactive depression, his personality showed no significant defects.

Numerous laboratory studies were done in an effort to evaluate his present status. A battery of liver function tests revealed no abnormality, except for a slightly lowered ratio of albumin to globulin (3.3/3.2). His basal metabolic rate was normal; no lipemia was present. An electrocardiogram showed diphasic P_2, but no other abnormality. The heart was normal by X-ray. The urine frequently contained small amounts of acetone. An electroencephalogram was normal.

Fasting blood sugar values ranged from 50 to 69 mg. %. An oral glucose tolerance test showed a delayed fall in that the 2 hour specimen contained 172.5 mg. % of glucose. The 3- and 4-hour specimens showed normal values. Simultaneous determinations of potassium and phosphorus were done. As expected in normal persons a fall from 4.88 to 4.25 meq/L occurred in the serum K, and the blood inorganic P fell from 3.73 to 3.24 mg. % during the test. Galactose and levulose tolerance tests showed that the patient was able to take up these sugars in a normal fashion. An epinephrine tolerance test was carried out with distinctly abnormal results. This will be discussed later.

This patient was also given a trial on adrenocorticotropic hormone. Qualitatively normal metabolic responses were observed, including gain in weight, depression of the eosinophil count, and increased output of urinary 17-ketosteroids. A metabolic balance study of minerals and nitrogen was carried out, but the patient was suspected of obtaining extra food, so the results are not considered entirely accurate. No change in the liver size, nor general condition of the patient, was

noted. A rise in blood glucose occurred above that seen in the preliminary period, but never to hyperglycemic levels. A dosage of 30 mg. every 6 hours was used. This would seem consistent with the previous observation in J. J. Although ACTH caused an elevation in fasting blood glucose, the degree of rise was less than expected at a given dosage level.

A biopsy of the liver was performed by Dr. Varco of the Department of Surgery. A sample of skeletal muscle was also obtained at this time. These specimens were quickly weighed and frozen. Dr. Gerty Cori of Washington University, St. Louis, performed studies of the glycogen and enzyme content. Her report showed the glycogen content of the liver to be 10.3 % of the wet weight. The muscle contained 2.58 and 1.88 % on 2 spearate aliquots. Her concluding comments were as follows: "The diagnosis of glycogen storage disease of the liver was thus confirmed. The muscle glycogen content was also high and somewhat beyond the level observed in normal human muscle. Enzymatic analysis of both liver and muscle glycogen revealed no gross abnormalities of structure. The specific glucose-6-phosphatase in the liver was strongly active, quite in contrast to the two von Gierke patients who died in infancy and in whose livers the enzyme was hardly active at all; in one of these cases, both biopsy and autopsy samples were studies with similar results. In two other cases of glycogen storage disease, who were doing well, both older children, the phosphatase was at a moderately subnormal level".

One wonders whether the normal enzyme content is responsible for, or the result of, our patients attaining adulthood. The first patient reported by Parnas and Wagner[1] reached adulthood and improved, although he then became diabetic.

Our third patient with von Gierke's disease, ., was admitted to University Hospitals at 2 years of age. Her abdomen had been large since birth and she had had frequent bouts of fever. Her parents were concerned because she was unable to walk, although her intelligence seemed normal by other criteria. She developed fever and jaundice in the first week of life. Jaundice had persisted 3 weeks. She vomited frequently in the first year of life and ate poorly. She perspired very profusely, and had a persistent skin rash. Her weight gain was good. The family history was not remarkable, except for extreme obesity of the mother. No convulsions had occurred.

Examination revealed a 2-year-old child of normal size (11.9 Kg. 32 inches). The abdomen was protuberant. There was diffuse miliaria and marked hyperhydrosis. The liver edge extended 5 cm. below the right costal margin and could easily be felt.

When drawn, the blood appeared lipemic. The total serum lipids were 180 turbidity units (normal 16-35) and the total cholesterole was 401. mg/100 ml. Although acetone was not found in 2 routine urine specimens, it appeared in large amounts when epinephrine was given. A depression of blood CO_2 content to 17 mmol./l was found on 2 occasions with normal serum Cl. The serum Na was also low. Blood ketones were not measured. Ketonemia without ketonuria has been reported in von Gierke's disease. An elevated sedimentation rate and an abnormal ratio of albumin to globulin (3.8/4.0) were the only other abnormal tests of liver function. Other tests, including prothrombin time, thymol turbidity, bromsulf phthalein retention, alkaline phosphatase, and cholesterol ester determination were within normal limits.

Fasting hypoglycemia was not found; the values for blood glucose ranged from 49.5 to 64 mg. %. A glucose tolerance test showed a delayed fall in blood glucose; three hours after the test dose of glucose, 136 mg. % remained in the blood. An epinephrine-glucose tolerance test showed only a very slight rise in blood glucose, and produced marked acetonuria. Galactose and levulose tolerance tests demonstrated the patient's ability to handle these sugars normally.

Although the child presented most of the clinical criteria of glycogen storage disease of the liver, the final proof of this would be the demonstration of the abnormal liver cells packed with glycogen. Storage of fat in the liver without abnormal glycogen, as well as cirrhosis, can closely simulate the clinical picture of von Gierke's disease. At our request, a biopsy of the liver was performed under general anesthesia by members of the Department of Surgery. Specimens from the pancreas, skeletal muscle, and skin were also obtained. The patient did poorly after surgery and expired on the second post-operative day.

Biopsy and autopsy examination of the liver showed the organ to be tremendously enlarged. It was yellow in color, and the cut surface exuded a creamy material. Microscopic examination of the liver showed extremely vacuolated hepatic cells with hydropic cytoplasm. The nuclei were uniform, small, and oval. Multiple small cytoplasmic vacuoles as well as large droplets were seen. Glycogen stains reveal the cells to be filled with pink stainign material (glycogen). A deficiency of beta cell granulation, but no abnormality of the alpha cells was seen in the pancreas. Skin and muscle were normal. The diagnosis of von Gierke's glycogen storage disease plus fatty infiltration of the liver was made.

Injection of epinephrine causes, along with its other effects, a transitory rise in blood sugar. In the normal fasting child, this rise is 30 to 45 mg. % and occurs in the first hour after administration. A rise of less than 20 mg. % is definitely abnormal. The rise in blood sugar is dependent upon both glycogenolysis and a decrease in peripheral tissue utilization of glucose[11]. Liver disease or caloric starvation resulting in low liver glycogen may cause a poor response, as well as a liver loaded with glycogen that cannot be released. This test has been considered diagnostic of glycogen storage disease of the liver, but obviously it is not if this phase of the test is done, alone. Along with other bodily states that demand rapid turnover of liver glycogen (e.g. fasting, glucose or insulin tolerance tests) the epinephrine test almost uniformly causes acetonuria in patients suffering from von Gierke's disease of the liver. This is not true of other liver diseases, including galactosemia.

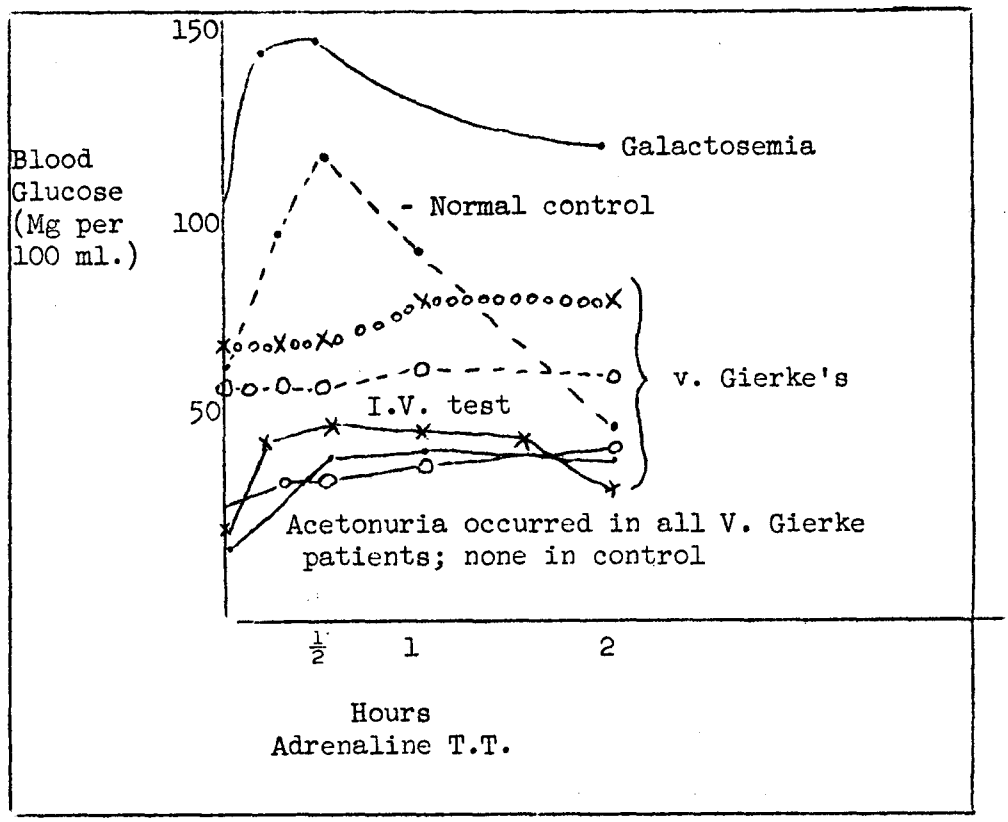
Standard epinephrine tests using 0.03 mg. per Kg of body weight injected subcutaneously were given to patients J. J. and L. F. Because D. B. was an adult, a total dosage of 1 mg. was used. Because poor absorption of the epinephrine could also cause a failure of response, J. J. was also tested by giving her test dose in an intravenous infusion of saline over a period of one hour. Although this test produced a greater rise in blood glucose, it was still less than normal.

As seen in figure 1, all patients with glycogen storage disease showed some rise in blood glucose following epinephrine, but less than the normal. Perhaps, more important was the marked acetonuria that each patient with glycogen storage disease developed during the test. None of the patients showed acetone in the urine immediately preceeding epinephrine injection. For comparison, the blood glucose values of a normal child and patient (galactosemia) are shown. Neither of these children developed acetonuria. It may, therefore, be concluded that all three of the first described patients fit the clinical criteria of the "classical von Gierke type" of glycogen storage disease of the liver. Histological appearance of the liver in each case confirmed this diagnosis.

Hyperglycemic factor

In 1923, Murlin and co-workers[12] found that a material could be obtained from the pancreas which produced hyperglycemia. Further studies have shown that commercial insulin prepared by several methods is capable of producing a transient rise in blood sugar, which preceeds the usual hypoglycemic effect when the insulin is given intravenously. That diabetic persons[13] and dogs[14] require larger main-

Figure 1



Failure of Blood Glucose to Rise After Epinephrine in V. Gierke's Disease

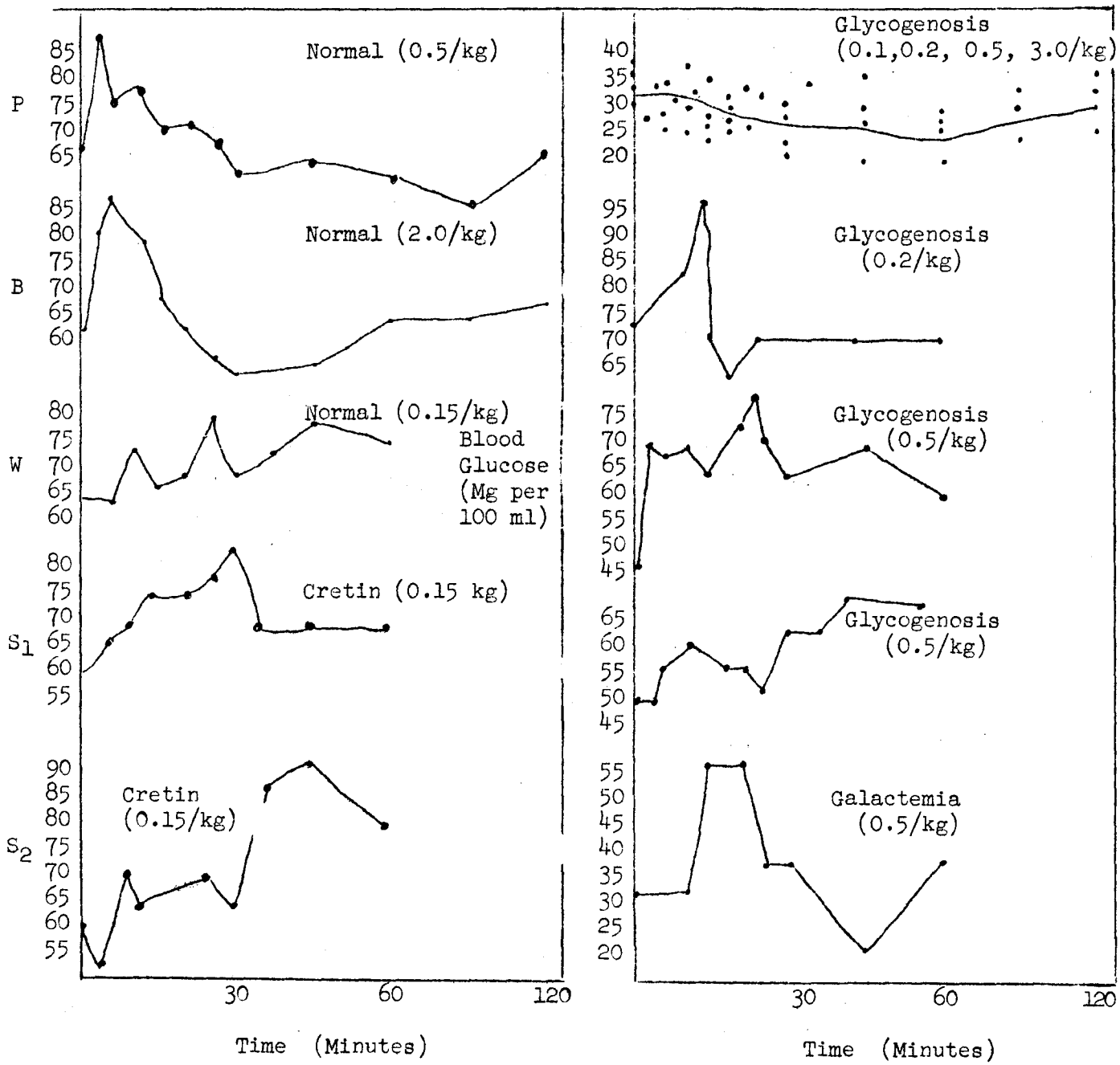
tainance dosages of insulin than their diabetic-depancreatized counterparts has been demonstrated, and suggests that a product of the pancreas is responsible for the insulin resistance. DeDuve, Hers, and Bouchart have shown that glycogenolysis occurs in the first few minutes after insulin injection[15]. DeDuve and Sutherland have obtained strong evidence that the origin of this hyperglycemic-glycogenolytic substance is the alpha cell of the pancreatic islets[16]. McQuarrie and collaborators have reported 2 patients[17] suffering from non-Addisonian hypoglycemosis whose alpha cells were missing or very deficient in number. Dr. S. H. Armstrong as quoted by Dr. Zimmerman[18] has suggested that the clinical entity resulting from a deficiency in the alpha cells may be von Gierke's disease. It has occurred to us that a failure of normal response to the alpha cell substance, though produced normally, might also result in glycogen storage disease. This state would be analogous to the Seabright-Bantam syndrome of pseudohypoparathyroidism of Albright.

Amorphous regular insulin may be treated with cysteine to reduce disulfide linkages, yielding a product which retains the hyperglycemic, but very little of the hypoglycemic activity originally present[19]. Dr. B. Zimmerman supplied the material for testing our first patient ( ) and demonstrated its potency on normal dogs. Since that time we have prepared the material from regular insulin in our laboratory. The freshly prepared powder was diluted with sterile water and sterilized by Sietz filtration. Each lot was tested for potency in normal children, after being cultured to demonstrate its sterility. Dry material which had been put into solution was discarded after a few days, although no studies have been done to show that

deterioration does occur in solution. The test subjects were given no food or water for at least 6 hours before the test periods. In most patients, the test was performed in duplicate on successive days. Since no dosage standards were available, we began with 0.1 mg/Kg of body weight and have given dosages as large as 5 mg/Kg. No untoward reactions have occurred. Blood samples were obtained at frequent intervals for one hour. Both macro and micro specimens have been used, and analyzed by the method of Nelson to obtain true blood glucose values[20].

Figure 2

Hyperglycemic Fraction of Insulin



In 6 tests on essentially normal patients, the rise in blood gulcose over pre-injection levels averaged 25 mg. %. The range was from 15 to 44 mg. %, representing rises of 22 to 79% above initial levels. These rises were not well correlated with dosage, which ranged from 0.15 to 2.0 mg. per Kg. of body weight. The maximum rise was seen most frequently between 5 and 20 minutes, and with the exception of our test in a child with cretinism, always occurred before 30 minutes. The peak in the latter instance was at 45 minutes.

Four tests were performed on patient The dosage used was from 0.1 - 3.0 mg/Kg. Maximum rises in each test were 2.5, zero, 2.0 and 3.5 mg. % averaging 2.0 mg. % for the four tests. The average is a rise of 6.7 % over initial levels. Using either method of comparison, it is obvious that this failure of the blood sugar to rise is significant. Two tests performed on D.B., using dosages of 0.2 and 0.5 mg. per Kg. of cysteine inactivated insulin, were normal. The former showed a rise of 24 mg.% or 34.3% above the initial level. The latter test produced a rise of 25 mg. % which was 59% above fasting. Maximum rises occurred at 13 and 24 minutes. A single test on using 0.5 mg. per Kg. gave a maximum rise of 17.5 mg.% at 40 minutes. This represents a rise of 34% over the fasting level. These two patients with von Gierke's disease responded to the hyperglycemic factor in a normal manner. (See Table I)

Thus, it appears that patient , with a proven diagnosis of glycogen storage disease of the liver, failed to respond to the hyperglycemic-glycogenolytic fraction of insulin in a normal manner, suggesting that she is refractory to the actions of this substance.

TABLE I

Effects of Hyperglycemic-Glycogenolytic Factor on Blood Glucose

Pt	Dose mg/kg	Glucose rise mg.%	No. tests	% rise above initial level	Time of max. rise
Normals	0.15-2.0	15-44 (av. 25)	6	22 - 79	5 - 45 min.
v. Gierke's					
	0.1 - 3.0	0 - 3.5	4	0 - 6.7	10 - 120 min.
	0.2 - 0.5	24, 25	2	34 - 59	13, 24 min.
	0.5	17.5	1	34	40 min.

B. Galactosemia.

The essential feature in the pathogenesis of this clinical entity is a congenital deficiency in carbohydrate metabolism characterized by inability to utilize galactose. Normally, galactose is readily converted into glucose by the liver. There such glucose may be converted into glycogen or be made available for oxidation in various tissues of the body. The defective step in the metabolism of the patient with galactosemia is that involved in the conversion of galactose to glucose, which is easily demonstrated by the galactose tolerance test.

The clinical features characterizing the syndrome are, 1. hepatomegaly, 2. failure of physical growth, 3. retardation of mental development, 4. proneness to the development of cataracts, 5. hypergalactosemia and galactosuria when the patient is maintained on a milk-containing diet (galactose from lactose). Although the total blood sugar is usually high in this condition, the fermentable fraction (glucose) tends to be low, in some instances to the point of true hypoglucosemia. Normocytic anemia and mild albuminuria are frequently present.

A typical case, ., who was a two month old female infant, was studied in the University Hospitals during the past year. Most of the foregoing features were present in this case. Hepatomegaly was evident. Changes in the eyes were described by a member of the staff in Ophthalmology as lenticonus. Galactosemia, galactosuria and mild albuminuria were constantly present, so long as milk formed the basis of her diet.

The patient's weight was said to have been stationary since birth. The hemoglobin was 10 Gm. per 100 cc of blood. The maternal grandmother was said to be a diabetic and one paternal grandparent was known to have sugar in the urine. One uncle on the father's side was said to have had a disorder during early infancy similar to that of our patient. Because he "could not take" milk, this was early withdrawn from his diet after which he thrived.

As indicated in the accompanying figures (Figs. 3 and 4), sugar tolerance tests showed marked impairment in the utilization of galactose while the glucose curve was normal. Both parents showed galactose tolerance tests which were interpreted as indicating impaired tolerance for this sugar, when compared with tests made at the same time on two normal control subjects. (Fig. 5)

An insulin tolerance test showed no increase in sensitiveness to this hormone, so far as blood glucose response was concerned. After an initial rise, the blood galactose curve declined in parallel with the glucose curve. (Fig. 3) In response to a single intravenous injection (0.5 mg. per kg) of the hyperglycemic, glycogenolytic factor separated from ordinary insulin ("alpha cell factor"), the blood glucose curve showed an essentially normal pattern, while the blood galactose curve at the same time showed the bizzare shape indicated in Fig. 2. ACTH had no definitive influence on the galactose tolerance curve (Fig. 4).

Following a preliminary period of clinical and physiological study with the patient being maintained on an ordinary milk formula, she was placed on a diet which contained no milk (i.e. no galactose). This formula was designed to have the same caloric value and the same content of protein, carbohydrate, fat, vitamins and minerals as the milk diet. The protein of this diet was supplied as finely minced cooked beef muscle. The nutritive value of the latter diet has previously been shown by analytical and growth studies to be equal to that in which milk constitutes the basis of the diet[21]. Within one month after the milk-free dietary regimen was substituted for the regulary milk formula, the patient gained 600 grams, the first gain ever recorded for her since birth. Her spontaneous activity and alertness were markedly increased.

The fasting blood glucose level rose from the subnormal values recorded during the milk feeding period to the normal range of 65 to 105 mg. per cent. The galactose content had decreased but values still ranged in the vicinity of 50 mg. per cent, despite use of the galactose-free diet for one month. Why such levels should persist is not apparent. It has been suggested that galactose may be stored in large amounts in the liver in galactosemia[22]. There is no evidence that glucose is ever converted into galactose.

When the galactose tolerance test was repeated after the patient had been on the modified-meat, galactose-free diet for over one month, the reaction of the patient was severe. She became very irri-

Figure 3

Carbohydrate Tolerance Tests

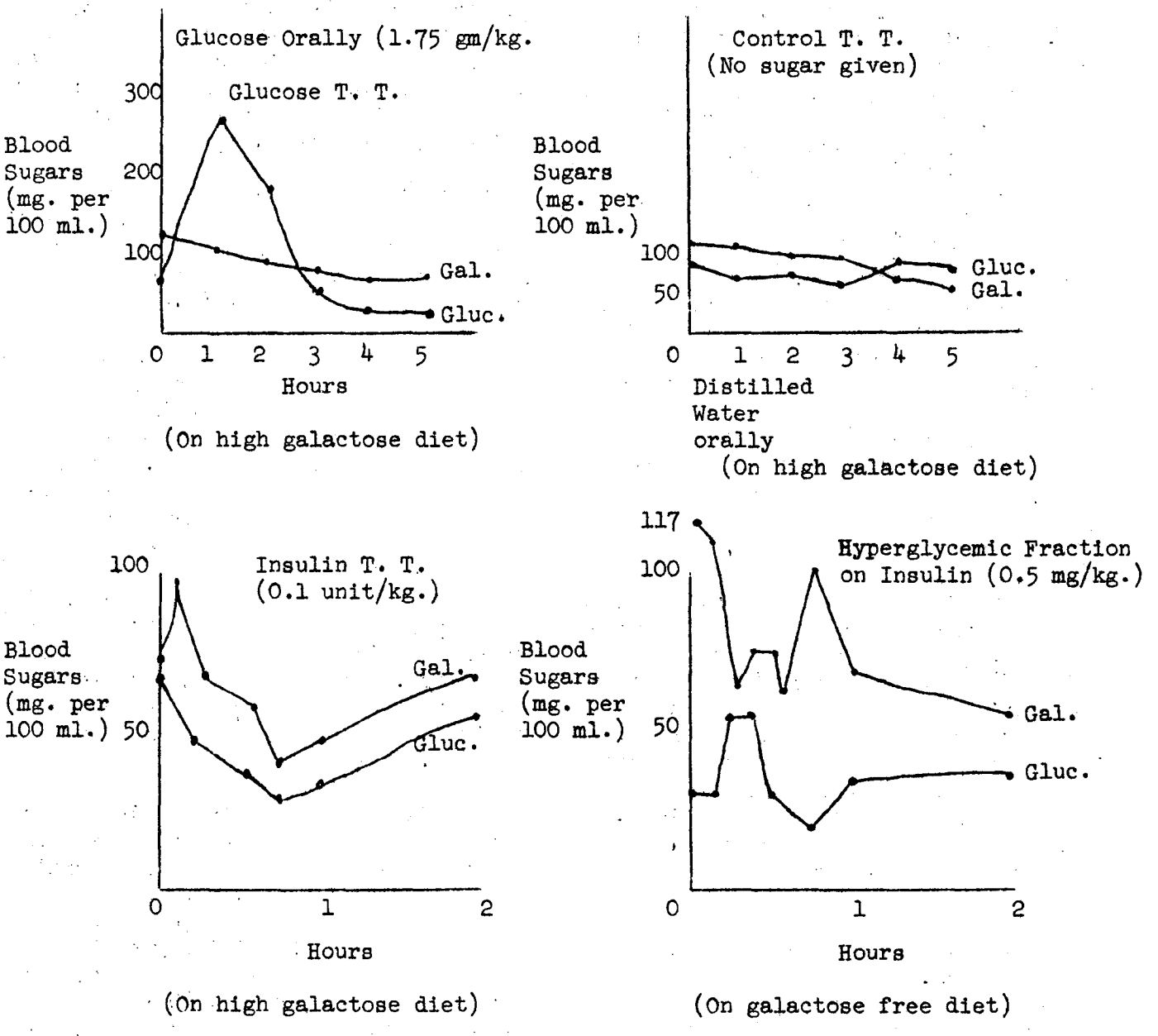
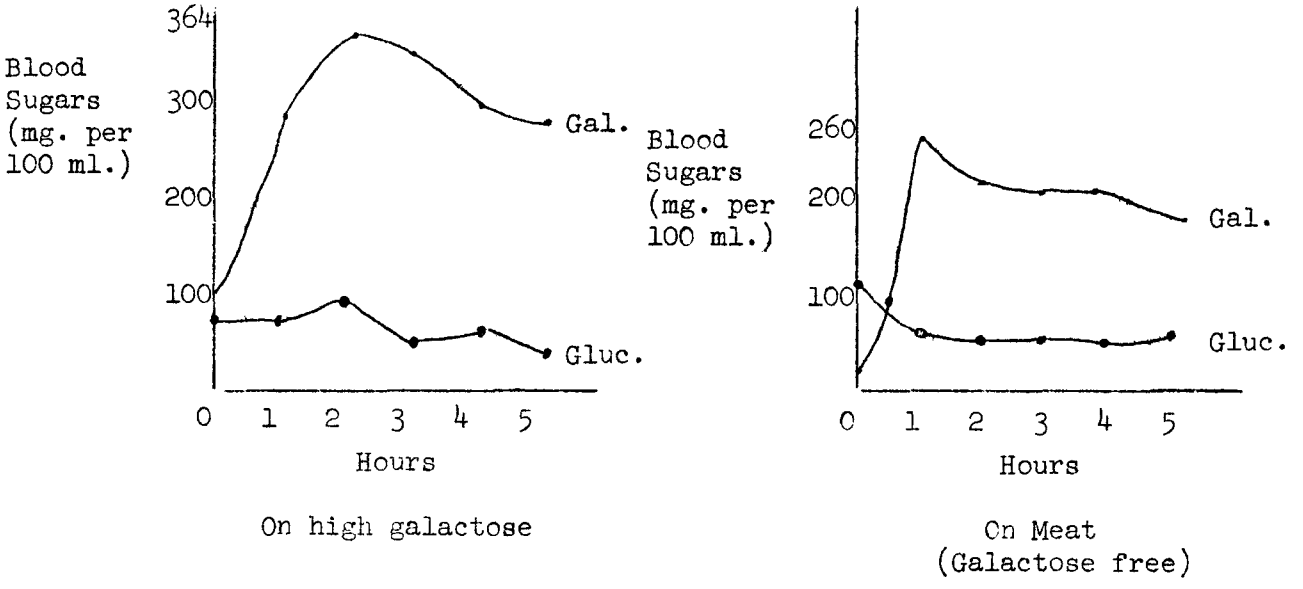


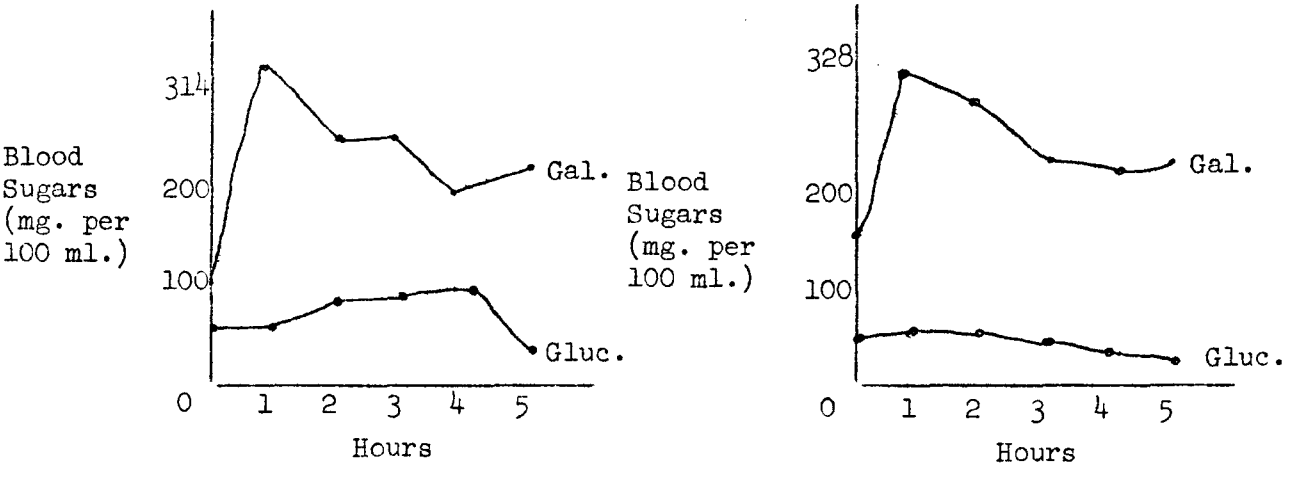
Figure 4

Galactose 1.75 gm/kg Orally



On high galactose

On Meat (Galactose free)



On ACTH 15 mg. q 6 h

On ACTH 30 mg. q 6 h

Figure 5

Mother and Father of
(40 gm. galactose orally)

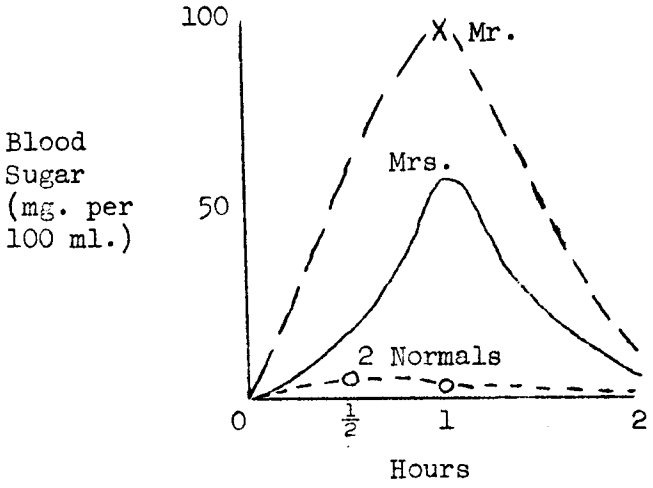


table and pale immediately and acted as if she were quite ill. Later she became somewhat lethargic and remained so for about 48 hours. The galactose administration had no such deleterious effects on any of the normal control subjects. The abnormal clinical reaction of the patient was accompanied by noticeable retention of sodium, potassium and chloride. The amount of K retained was out of proportion to the nitrogen. No comparable increase in retention of phosphorus occurred, which indicates that these retentions were not due to glycogen deposition. Water retention accompanied the other changes. These abnormal reactions strongly suggest that galactose is peculiarly toxic for patients afflicted with galactosemia.

Since several independent investigations[23,24] into the pathological state of the liver have revealed excessive amounts of fat deposited in the liver, with a normal or decreased glycogen content, it would not seem justifiable to include these cases in the category of glycogen storage disease. That the hepatic cirrhosis described in some patients afflicted with galactosemia may be due to the toxic action of galactose is not unthinkable.

Fortunately, the early recognition of the disorder and proper prophylactic use of the milk-free (galactose-free) dietary regimen may permit essentially normal growth and development[25]. The present report would appear to confirm this observation so far as it goes.

As regards the nature of the underlying physiological abnormalities responsible for the clinical and pathological changes observed in essential glycogenosis or von Gierke's glycogen storage disease and in galactosemia, the most promising approach for investigation appears to be that involving the enzyme systems governing the intermediary carbohydrate metabolism. Much may be expected from future research in this field.

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II. MEDICAL SCHOOL NEWS

Coming Events

October 16-18	Continuation Course in Treatment of Diseases of the Chest for General Physicians
October 17	American Trudeau Society Lecture; "The Effects of BCG Vaccination in Silicotic Animals," Dr. Arthur J. Vorwald, Director, The Trudeau Foundation and the Saranac Laboratory, Saranac Lake, New York; The Nicollet Hotel; 8:00 p.m.
October 20-25	Continuation Course in Gastro-Intestinal Roentgenology for Radiologists
October 21	The Minnesota Pathological Society Lecture; "Hypothermia and Cardiac Surgery," Dr. F. John Lewis, Associate Professor, Department of Surgery; Owre Amphitheater; 8:00 p.m.
October 22	Leo G. Rigler Lecture; "X-ray Diagnosis of Diseases of the Gallbladder," Dr. B. R. Kirklin, Professor, Department of Radiology, Mayo Foundation, Rochester; Museum of Natural History Auditorium; 8:00 p.m.
October 30-31	Continuation Course in Medical Economics for Physicians
Oct. 31 - Nov. 1	Special Homecoming Program for Physicians
November 13-15	Continuation Course in Fractures and Surgery of Trauma for General Physicians

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Minnesota Medical Foundation Day Activities

On Thursday, October 2, the Minnesota Medical Foundation once again presented its annual Foundation Day program. At 4:30 p.m. in Owre Amphitheater, thirteen scholarships of $500.00 each were awarded to deserving students. Seven of these scholarships were awarded to members of the present sophomore and junior classes: Charles Gamble, Barbara Hanson Subak, Karl Palmer, Bertrum Woolfrey, Gene E. Meger, Robert Radke, and Maynard Jacobson. Six additional scholarships were presented to freshmen entering the Medical School for the first time this fall. These scholarships were made possible through the efforts of Dr. Donald J. Cowling and were made available to graduates of state colleges in Minnesota. The recipients of these scholarships were: Duane Flogstad, Eugene W. Hanson, Harlis Hanson, Gerald Kuss, Curtis Stolee, and Ernest Swanson.

Following the presentation of the scholarships, students and members of the staff were privileged to hear Dr. William S. Middleton, Dean of the University of Wisconsin Medical School, deliver the annual Foundation Day lecture. His address, "The Springs of Medical Strength," was stimulating and inspiring to all who heard it.

Members of the Foundation, their guests, and the recipients of the scholarships gathered at the Campus Club at 6:15 for the annual dinner meeting. After an excellent dinner, the report on the activities of the Membership Committee was given by Dr. Francis W. Lynch, Vice-President of the Foundation. Dr. Lynch emphasized the fact that Dr. Vernon D. E. Smith and other members of the membership committee have been very active in speaking to groups of physicians at county medical society and hospital staff meetings concerning the objectives of the Foundation. He noted also that there has been a marked increase in the number of Patron members.

The Nominating Committee report was given by Dr. R. S. Ylvisaker. Those nomi-

(Continued on next page)

nated for the Board of Trustees for the period 1952-1956 were Dr. Moses Barron of Minneapolis, Dr. Ray Hedin of Red Wing, and Dr. Herman E. Drill of Hopkins. These nominations were seconded and approved. These three physicians succeed as members of the Board of Trustees Doctors Russell Moe, William Hanson, and Charles Code, all of whom have shown a real and active interest in the work of the Foundation.

Mr. Nathan Sidley, a senior medical student, reported on the activities of the Student Advisory Committee. He pointed out the very real accomplishments of this group in the last year such as the development of the freshman orientation program and discussed aims for the future.

Following the introduction of the scholarship recipients to the group, the meeting closed with a memorable impromptu talk by Dr. Cowling concerning the American system of education in general and the problems that confront medical education in particular.

Faculty News

The Medical School faculty was saddened during the summer months by the serious illness of Dr. Saul L. Cohen, Associate Professor of Physiological Chemistry. We are all heartened by the fact that he has recently been discharged to his home, and we all join in expressing our hopes for his speedy recovery.

Dr. W. D. Armstrong, Professor and Head, Department of Physiological Chemistry, has for the past five years been serving on the Dental Studies Section of the U. S. Public Health Service. His term has now expired and he has been appointed to the Advisory Council to the Surgeon General.

Dr. William J. Simon, Professor of Dentistry at the University of Minnesota, has been named Dean of the College of Dentistry at the State University of Iowa at Iowa City. Dr. Simon, who has been on the staff of the University of Minnesota School of Dentistry since 1936, will take over his new duties on January 1, 1953. The entire faculty of the Medical School joins in offering congratualtions and best wishes to Dr. Simon in his new post.

Dr. David Glick, Professor of Physiological Chemistry, recently attended the meeting of the American Chemical Society in Atlantic City, New Jersey. On September 16, Dr. Glick presented the first Ernst Bischoff Lecture to that group. His subject was "Extrapolation into the Future of Clinical Microchemical Analysis."

Dr. David State, formerly Associate Professor of Surgery, has resigned as a member of the staff of that department and has left Minneapolis because of ill health in his family. He plans eventually to enter practice in California. We regret losing Dr. State from our faculty, but join in extending him our best wishes for future success. His position as Director of the Cancer Detection Center will be held by Dr. Claude R. Hitchcock, Instructor in Surgery, to whom we offer our congratulations on his new appointment.

Doctors Howard L. Horns, Carleton B. Chapman, and Robert B. Howard of the Department of Medicine spent the weekend of September 27 and 28 in Huron, South Dakota, where they presented a two-day postgraduate seminar on various medical subjects to the members of the South Dakota Chapter of the American Academy of General Practice.

Dr. W. A. Fansler, Clinical Associate Professor of Proctology, attended the recent meeting of the American Board of Proctology which was held at the Warwick Hotel in Philadelphia on September 26, 27, and 28.

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

October 13 - 18, 1952

Monday, October 13

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Physiology Seminar; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - 5:30 Seminar on Fluid and Electrolyte Balance; Gerald T. Evans; Todd Amphitheater, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

4:30 - 6:00 Physiology 114A and Cancer Biology 140 -- Research Conference on Cancer, Nutrition, and Endocrinology; Drs. Visscher, Bittner, and King; "Causes of Death in Mice," J. T. King; 129 Millard Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Ancker Hospital

8:30 - 10:00 Chest Disease Conference.

Monday, October 13 (Cont.)

Ancker Hospital (Cont.)

1:00 - 2:00 Medical Grand Rounds.

Veterans Administration Hospital

8:00 - 9:00 Neuroradiology Conference; J. Jorgens, R. C. Gray; 2nd Floor Annex.

9:00 - G. I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; J. Jorgens, Conference Room, Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; C. K. Aldrich; Bldg. I.

Tuesday, October 14

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Physiology 114D -- Current Literature Seminar; 129 Millard Hall.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases from Minneapolis General Hospital; Drs. Lipschultz and Blank; Eustis Amphitheater, U. H.

Ancker Hospital

8:00 - 9:00 Fracture Conference; Auditorium.

8:30 - 9:30 Medical-Roentgenology Conference; Auditorium.

1:00 - 2:30 X-ray - Surgery Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

12:30 - Grand Rounds; Fractures; Sta. A; Willard White, et al.

12:30 - Neuroroentgenology Conference; O. Lipschultz, J. C. Michael and Staff.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Cal, and Lipschultz

Tuesday, October 14 (Cont.)

Minneapolis General Hospital (Cont.)

1:00 - Neurology Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; L. J. Hay, J. Jorgens; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Autopsy Conference; E. T. Bell and Donald Gleason, Conference Room, Bldg. I.

Wednesday, October 15

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wnagensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Radioisotope seminar; Incorporation of P^{32} during liver regeneration; C. P. Barnum; 12 Owre Hall.

1:30 - 3:00 Physiology 114B -- Circulatory and Renal Systems Problems Seminar; Dr. M. B. Visscher, et al; 214 Millard Hall.

4:00 - 5:30 Physiology 114C -- Permeability and Metabolism Seminar; Nathan Lifson; 214 Millard Hall.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

Wednesday, October 15 (Cont.)

Ancker Hospital (Cont.)

2:00 - 4:00 Medical Ward Rounds;

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:00 - Surgery-Physiology Conference; Drs. Zierold and E. B. Brown; Classroom.

12:30 - Pediatric Conference; Oxygen Therapy; William Kubicek; Station I, Classroom.

1:30 - Visiting Staff Case Presentation; Station I, Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, October 16

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Strangulation Obstruction; Harry Z. Mellins; Eustis Amphitheater, U. H.

Thursday, October 16 (Cont.)

Medical School and University Hospitals (Cont.)

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

4:00 - Medical Pathological Conference; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

Friday, October 17

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Surgery of Congenital Heart Disease; C. Walton Lillehei; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Physiology 124 -- Seminar in Neurophysiology; Ernst Gelhorn; 113 Owre Hall.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Friday, October 17 (Cont.)

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I., Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - X-ray Conference; Oscar Lipschultz; Classroom, Main Building.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

Saturday, October 18

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; Some Effects of Cortisone on the Hepatic Parenchyma of Rabbits; W. L. Williams; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - 12:00 Medical - X-ray Conference; L. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Hagen, Goldish, and Aufderheide
11:15 - 12:00 Morphology . . . . . Dr. Aufderheide