MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

November 7, 1963

GLYCOGEN STORAGE DISEASES

Case 1: HEPATO-RENAL TYPE (VON GIERKE'S DISEASE) ([redacted])

The patient is a 4 year old [redacted] girl who was noted shortly after term delivery to have a large abdomen with thin spindly extremities. She seemed to grow slowly as compared to her normal older brother. At age 6 months, she developed bronchopneumonia, followed by persistent diarrhea and vomiting which continued for a period of at least 2 to 3 weeks. At age 9 months, she was placed on a relatively low fat diet and her general condition improved. When the patient was 22 months old she was admitted to the [redacted] for study and was at that time noted to have marked hepatomegaly without splenomegaly. Abnormal blood chemistries included a fasting blood sugar of 45.2 mg.%; and SGOT of 94; a glucose tolerance test showed persistent elevation after 2 hours; and epinephrine response test demonstrated no significant response of blood sugar to a test dose of epinephrine. (Figure 1).

A needle biopsy of the liver showed enlargement of all cell types with PAS positive material present in a number of the cells. On the basis of these findings the pathologic diagnosis of von Gierke's disease was made.

A glucose-6-phosphatase assay of the liver biopsy material was carried out by Dr. Henry Kirkman and a glucose-6-phosphatase activity of less than 25 μgm of phosphorus per 100 mg of liver per hour was detected. Normal range is 250-450 μgm/100 mg/hr. She was treated with frequent feedings of a high protein diet.

The patient was seen at [redacted] in [redacted] 1963 at age 3-1/2 years because of fever of unknown origin. Physical examination was completely negative except for a liver enlarged 7 cm below the right costal margin. The child was comsidered to be of normal height and weight for her age. Heart was not enlarged; spleen and kidneys were not palpable. Muscle strength was normal. A glucose tolerance test at that time showed a fasting level of 58 mg.% and a persistent elevation (Figure 2). The patient became afebrile without specific therapy and discharged when on [redacted]/63 she was asymptomatic.

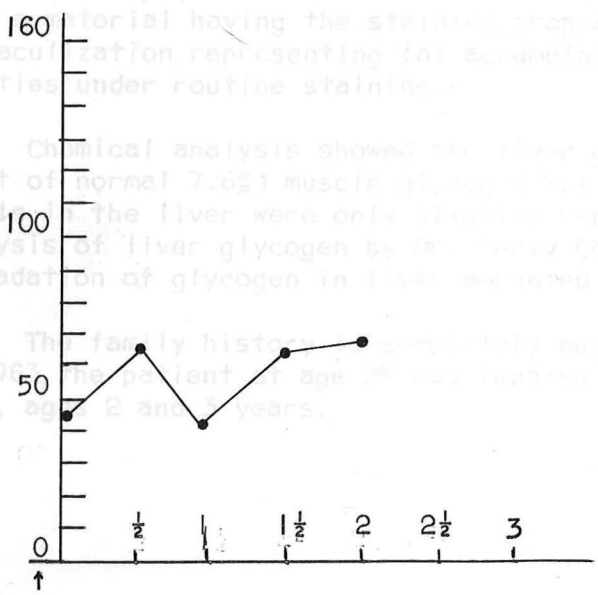


Fig. 1 Adrenalin Response Test

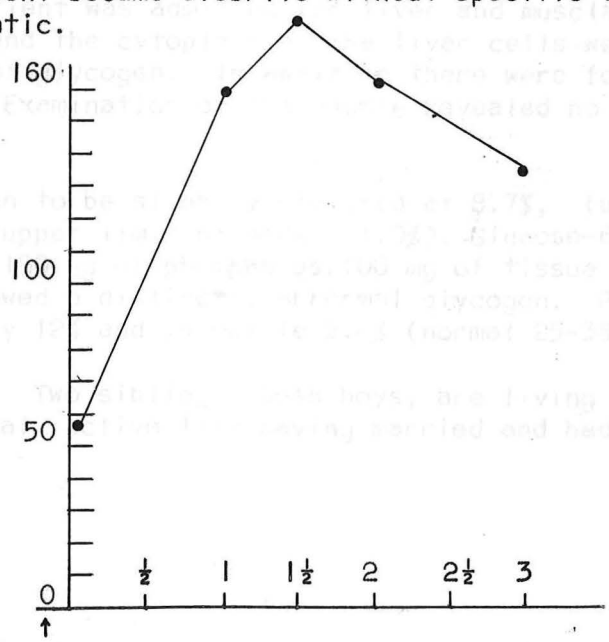


Fig. 2 Glucose Tolerance Test

Case 2: CARDIAC TYPE (POMPE'S DISEASE) [redacted]

The patient was a [redacted] male infant admitted to [redacted] at the age 10 days. Shortly after a term delivery the infant was noted to have respiratory distress and X-ray revealed cardiomegaly and patchy infiltrate in the left upper lung field which was diagnosed as bronchopneumonia. Jaundice appeared on the second day, billirubin rising to 14.5 mg.%. The patient was treated with penicillin and streptomycin and discharged on the 5th day of life. Five days later he was referred to [redacted] because of persistent cardiomegaly. Examination revealed persistence of icterus; massive cardiomegaly and tachycardia of 170-180; EKG showed PR interval of 0.08 second; no murmurs were heard. On admission the liver was palpated 2 cm below the right costal margin; however, this decreased somewhat in size during the first two days of hospitalization. His respiratory difficulty persisted and on [redacted]-62 a grade 2 harsh systolic murmur was heard over the pericardium. Despite digitalization, the respiratory difficulty continued. The liver continued to enlarge and following progressive respiratory distress the patient expired on [redacted]-62. At autopsy the heart was found to be markedly hypertrophy, weighing 30 grams (approximately twice the normal weight for this size infant). No significant valvular lesions were detected. Areas of vaculated cells were seen in the myocardium.

The patient has one normal sibling and both parents are well. There is, however, a history of two paternal cousins dying before the age of 6 months with hepatomegaly.

Case 3: LIMIT DEXTRINOSIS (FORBES' DISEASE) ([redacted])

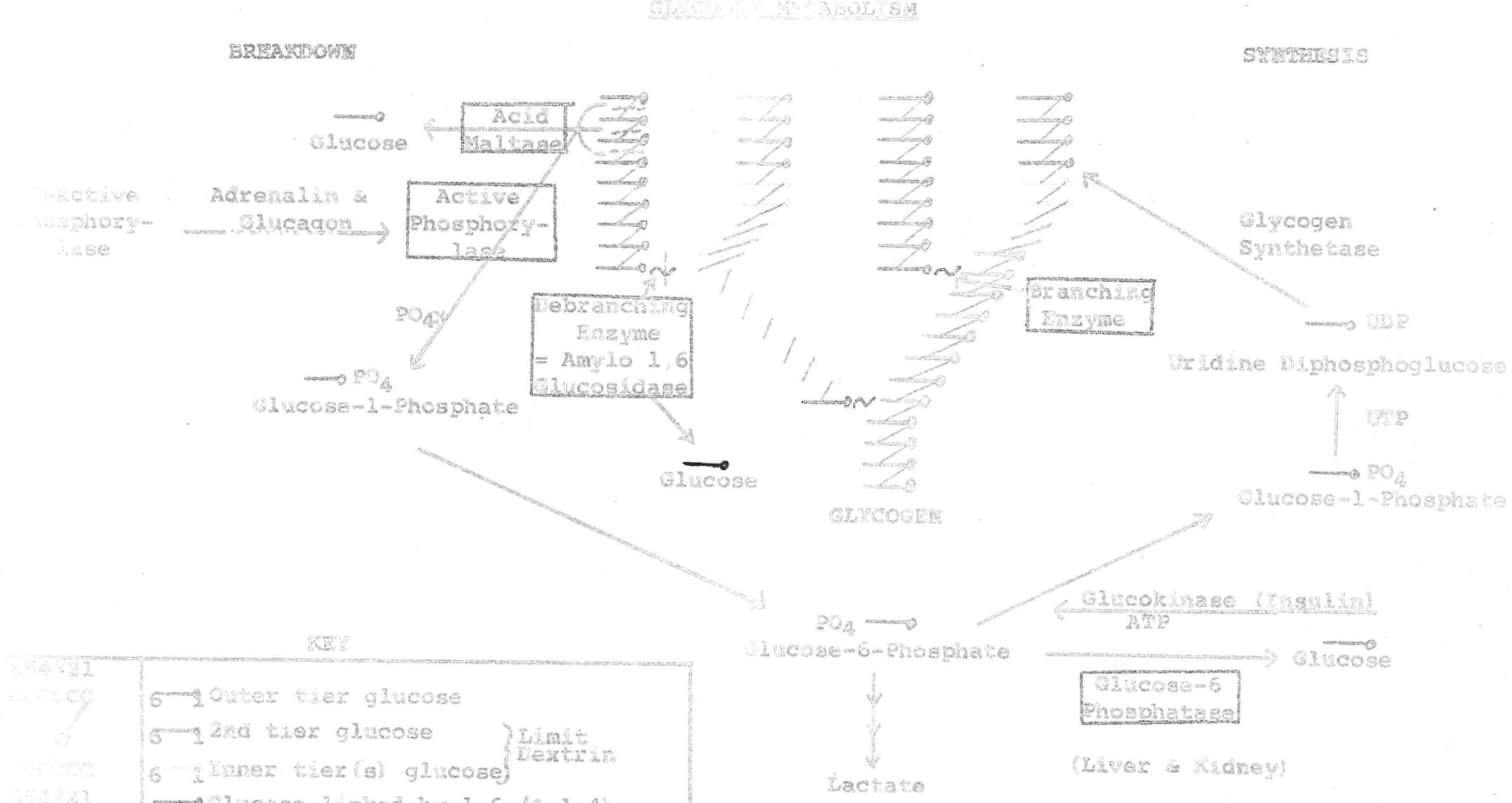
The patient is at present a 25 year old [redacted] girl who was first seen at [redacted] in 1942 at the age of 3-1/2 years. She was noted at that time to have had asymptomatic swelling of the abdomen from the age of 1 year and on admission marked hepatomegaly was observed. All glucose tolerance tests showed persistent elevation of blood glucose for a four hour period. Laboratory findings on this admission showed a glucose of 42 mg.% an elevation of total lipids of 2.22 grams %. The serum cholesterol was also increased to a value of 420 mg.%. The patient was followed in the outpatient clinic and persistence of the hepatomegaly was noted but she was completely asymptomatic.

In 1951 at the age of 12-1/2 years the patient was admitted for liver and muscle biopsy. The liver biopsy revealed that both the nuclei and the cytoplasm of the liver cells were packed with a material having the staining properties of glycogen. In addition there were focal areas of vaculization representing fat accumulation. Examination of the muscle revealed no abnormalities under routine staining.

Chemical analysis showed the liver glycogen to be slightly elevated at 8.7%, (upper limit of normal 7.6%) muscle glycogen was 4.6% (upper limit of normal 1.0%). Glucose-6-phosphatase levels in the liver were only slightly reduced (180 μg of phosphorus/100 mg of tissue per hr.). Analysis of liver glycogen by Dr. Gerty Cori showed a distinctly abnormal glycogen. Phosphorylase degradation of glycogen in liver amounted to only 12% and in muscle 2.6% (normal 25-38%).

The family history is completely negative. Two siblings, both boys, are living and well. In 1963 the patient at age 25 was leading a normal, active life having married and had two sons, ages 2 and 3 years.

GLYCOGEN METABOLISM



TYPES OF GLYCOGENOSES

Cori Type	Eponym	Clinical Names	Organs Involved	Glycogen Structure	Enzyme Defect
I	von Gierke's Disease	Hepato-renal Type	Liver Kidney	Normal	Glucose-6-phosphatase
2	Pompe's Disease	Cardiac Type, or Generalized Glycogenosis	All Tissues	Normal	Lysosomal Acid Maltase
3	Forbes' Disease or Cori's Disease	Limit Dextrinosis	Liver (also skel. muscle, heart and probably other tissues)	Short, outer branches	Debranching Enzyme
4	Andersen's Disease	Amylopectinosis	Liver (also all tissues)	Long chains with few branches	Branching Enzyme
5	McArdle-Schmid-Pearson Disease	Muscle Phosphorylase Type	Muscle	Normal	Muscle Phosphorylase
6	Hers' Disease	Hepatic Phosphorylase Type	Liver	Normal	Liver Phosphorylase

Specific Types of Glycogen Storage Disease Can Probably Be Diagnosed from Blood Analyses Alone

1. von Gierke's Disease

   Platelet glycogen is specifically elevated. Ref. 19

2. Pompe's Disease

   Leukocyte glycogen is increased.

3. Limit Dextrinosis (Forbes' Disease)

   a. Red blood cell glycogen is greatly increased only in this type. Ref. 33

   b. Leukocyte debranching enzyme is decreased.
   Williams, H.E , Kendig, E.M. and Field, J.B
   Leukocyte Debranching Enzyme in Glycogen Storage Disease
   J. Clin. Invest. 42:656, 1963.

4. Amylopectinosis (Andersen's Disease)

   Iodine spectra of glycogen is abnormal in red blood cell.
   Refs. 34, 36.

5. Hepatic Phosphorylase (Hers' Disease)

   Leukocyte phosphorylase is decreased. Refs. 44, 45.

REFERENCES

General Reviews

*1. Stetten, D., Jr. and Stetten, M. R. Glycogen Metabolism. Phys. Rev. 40:505, 1960
Review of normal glycogen metabolism with (P. 529-534) an excellent brief discussion of glycogenoses.

*2. Field, R. A. Glycogen Deposition Diseases in The Metabolic Basis of Inherited Disease Stanbury, Wyngaarden and Fredrickson, P. 156-207 McGrall Hill, 1960
A complete review of the glycogenoses with a good section on the normal function and biochemistry of glycogen.

3. Illingsworth, Barbara. Glycogen Storage Disease. Am. J. Clinic. Nutr. 9:683, 1961.
A brief review primarily of the studies on glycogenoses carried out by the Cori group.

4. Cori, G. T. Glycogen Structure and Enzyme Deficiencies in Glycogen Storage Disease Harvey Lectures 48:145, 1954.
Cori, G. T. Biochemical Aspects of Glycogin Deposition Disease. Modern Problems in Ped. III:344, 1958
Descriptions of all of cases studied by Dr. Cori with emphasis on chemical changes.

5. van Creveld, S. The Clinical Course of Glycogen Disease. Can. J. Med. Assoc. 88:1,1963.
Historical and good clinical review especially of author's patients.

Hepato-renal Type (von Gierke's Disease)

6. van Creveld, S. Glycogen Disease. Med. 18:1, 1939.
Good clinical descriptions of the early cases of von Gierke's, van Creveld's and subsequent cases of glycogenosis. The summary P. 55-78 remains an excellent description of the symptomology of von Gierke's disease.

7. Mason, H. H. and Andersen, D. H. Glycogen Disease. Am. J. Dis. Child 61:795, 1941.
Report of a case of von Gierke's with a "pre-enzymologic" classification and excellent clinical description of glycogenoses, especially von Gierke's disease.

8. Cori, G. T. and Cori, C. F. Glucose-6-phosphatase of the Liver in Glycogen Storage Disease. J.Biol. Chem. 199:661, 1962.
In 4 cases of von Gierke's disease glucose-6-phosphatase was greatly depressed. The first demonstration that the absence of an enzyme is responsible for a disease.

9. Schulman, J. L. and Saturen, P. Glycogen Storage Disease of the Liver I. Clinical Studies during the Early Neonatal Period. Ped. 14:632, 1954.
Cori, G. T. and Schulman, J. L. Glycogen Storage Disease of the Liver, II. Enzymic Studies. Ped. 14:646, 1954.
Good clinical, pathologic and biochemical discussion of von Gierke's disease.

10. Lowe, C. U., Sokal, J. E., Doray, B. H. and Sarcione, E. J. Biochemical Studies and Specific Therapy in Hepatic Glycogen Storage Disease. J. Clin. Invest. 38:1021, 1959.
Marked decrease in liver size noted after glucagon therapy. C^{14} glucose is rapidly incorporated into liver glycogen in von Gierke's disease.

11. Hubble, D. Glucagon and Glycogen-Storage Disease of the Liver. Lancet I:235, 1954.
First demonstration that von Gierke's disease does not respond normally to glucagon.

12. Hug, G. Glucagon Tolerance Test in Glycogen Storage Disease. J. Ped. 60:545, 1962.
Description of "Double Glucagon Test". After 14 hour fast glucagon 0.7 mg/meter^2 I.V. gives no glucose rise in either Forbes' (Cori"s) disease or von Gierke's disease. After eating Forbes' disease becomes normal.

13. Schwartz, R., Ashmore, J., Renold, A. E. Galactose Tolerance in Glycogen Storage Disease. Ped. 19:585, 1957.
Patient with von Gierke's disease failed to show normal rise in blood glucose after galactose feeding, but galactose produced lactacidosis. A possible but potentially dangerous test for von Gierke's disease

14. Wagner, R. Glycogen Content of Isolated White Blood Cells in Glycogen Storage Disease. Am. J. Dis. Child 73:559, 1947.
First clear demonstration of increased glycogen content of leukocytes in a case of von Gierke's disease.

15. Howell, R. R., Ashton, D. M., Wyngaarden, J. B. Glucose-6-phosphatase Deficiency in Glycogen Storage Disease. Ped. 29:553, 1962.
Three children with von Gierke's disease had hyperuricemia and elevated serum lactic acid levels. (The hexose monophosphate pathway of glucose oxidation was active on in vitro assay of one liver.)

Adult von Gierke's Disease

16. Kolb, F. O., de Lalla, O. F. and Gofman, J. W. The Hyperlipemia in Disorders of Carbohydrate Metabolism. Metab. 4:310, 1955.
Report hyperurecemia and gout in two men with von Gierke's disease.

17. Holling, H. E. Gout and Glycogen Storage Disease. Ann. of Int.Med. 58:654, 1963.
A brother and sister both with von Gierke's disease developed hyperuricemia associated with lacticacidemia and gout. Died of uremia ages 36 and 40 years.

18. van Creveld, S. Glycogen Disease. Arch. Dis. Child 34:298, 1959
Followup of the original two cases of "von Gierke's" disease now ages 32(♀) and 38(♂) years. Livers were still slightly enlarged; epinephrine and glucagon tests still abnormal but patients otherwise normal with two normal sons (case 1♀) and one normal son (case 2♂).

Genetic Studies of von Gierke's Disease

19. Linneweh, F., Lohr, G. W., Waller, H. D. and Gross, R. Heterozyguten-Test für Glykogenose (v. Gieke's Krankheit). Klin. Wach. 41:352, 1963.
Glycogen content of blood platelets is consistently elevated in both patients with von Gierke's and in every heterozygous subject. Normal 26.4 ± 7.8 micromoles/10" platelets; von Gierke's 95 micromoles/10" platelets; Heterozyg 60 micromoles.

20. Hsia, D. Y. Y. and Kot, E. G. Detection of Heterozygous Carriers in Glycogen Storage Disease of the Liver (von Gierke's Disease). Nature 183:1331, 1959.
Discusses briefly the genetic basis for concluding von Gierke's disease is autosomal recessive trait. Presents a test for heterozygous carriers which is invalid.
See Ref. 21, 22.

21. Sokal, J. E., Fleissner, S., Sarcione, E. J. and Lowe, C. U. Blood Glucose-6-phosphate in Heterozygous Carriers and Patients with Liver Glycogen Disease. Nature 192:265, 1961.
Can find no difference in red blood cell glucose-6-phosphate levels between normal, diseased and heterozygous subjects.

22. Williams, H. E., Johnson, P. Fenster, L. F., Laster, L. and Field, J. B. Intestinal Glucose-6-phosphatase in Control Subjects and Relatives of a Patient with Glycogen Storage Disease. Metab. 12:235, 1963.
Glucose-6-phosphatase demonstrated in normal small intestine peroral biopsies. Level of enzyme probably decreased in both parents of patients with von Gierke's disease

Cardiac Type (Pompe's Disease)

23. di Sant'Agnese, P. A., Andersen, D., Mason, H. and Bauman, W. A. Glycogen Storage Disease of the Heart. I. Report of Two Cases in Siblings with Chemical and Pathologic Studies. Ped. 6:402, 1960.
First clear definition of Pompe's disease. Two definite and two probable cases described in one sibship. Presents a good clinical and pathologic description emphasizing that all tissues, not just heart, are involved.

24. di Sant'Agnese, P. A., Andersen, D., Mason, H. H. Glycogen Storage Disease of the Heart. II. Critical Review of the Literature. Ped. 6:607, 1950.
Review of the 14 known cases, as of 1950, of Pompe's disease. Outlines critical criteria for Dx.

25. di Sant'Agnese, P. A. Diseases of Glycogen Storage with Special Reference to the Cardiac Type of Generalized Glycogenoses. Ann. N. Y. Acad. Sc. 72:439, 1959.
Recent brief review of major features of Pompe's disease.

*26. Ehlers, K. H., Hogstrom, J. W. C., Lukas, D. S., Redo, S. F. and Engle, M.A. Glycogen Storage Disease of the Myocardium with Obstruction to Left Ventricular Outflow. Circ. 25:96, 1962.
Complete Review of world's literature on Pompe's disease (54 cases) as of 1962. Good description of clinical cardiac findings in their one case. Emphasized short PR interval on ECG as characteristic (17/21 of cases studied).

27. Ehlers, K. H., Engle, M. A.. Glycogen Storage Disease of Myocardium. Am. Hrt. J. 65:145, 1963.
Brief summary of cardiac signs of Pompe's disease.

28. Hers, H. G. α-Glucosidase Deficiency in Generalized Glycogen-Storage Disease (Pompe's Disease). Biochem. J. 86:11, 1963.
First demonstration of an enzyme defect in Pompe's disease. Acid maltase (α-glucosidase) of the lysosomes is markedly reduced. Discusses possible mechanism of pathology.

Limit Dextrinosis (Forbe's or Cori's Disease)

29. Forbes, G. B. Glycogen Storage Disease. J. of Ped. 42:645, 1953.
First description of a case of limit dextrinosis with clinical and chemical differentiation from van Gierke's disease.

30. Illingworth, B., Cori, G. T.. Structure of Glycogens and Amylopectins. J. Biol. Chem. 199:653, 1952.
The first demonstration that glycogen can be abnormal in structure in a glycogen storage disease (amylopectinoses).

31. Illingsworth, B., Cori, G. T. and Cori, C. G. Amylo-1,6-glucosidase in Muscle Tissue in Generalized Glycogen Storage Disease. J.Biol. Chem. 218:123, 1956
First biochemical demonstration of enzymatic lesion in Forbes disease (limit dextrinosis). Debranching enzyme is absent.

*32. Hug, G., Krill, C. E., Jr. Perrin, E. V., and Guest, G. M. Cori's Disease (Amylo-1,6-glucosidase Deficiency): Report of a Case in a Negro Child. N. Eng. J. Med. 268:113,1963.
Extremely well studied case of limit dextrinosis with complete biochemical and clinical evaluation.

33. Sidbury, J.B., Cornblath, M., Fisher, J., House, E. Glycogen in Erythrocytes of Patients with Glycogen Storage Disease. Ped. 27:103, 1961.
Erythrocyte glycogen is elevated only in Type III (limit dextrinosis) form of glycogen storage disease. Normal after 2 months 32-134 μg/gm Hb; Range in Forbes' disease 1,215 to 30,590 in 8 patients. Abnormality persists after adulthood. This is a simple and valuable test.

34. Sidbury, J. B., Gitzelmann, R., Fisher, J. The Glycogenoses. Further Observations on Glycogen in Erythrocytes of Patients with Glycogenoses. Helv. Paed. Acta. 16:506, 1961. Documents usefulness of red blood cell glycogen assay in diagnosis of Forbes and Andersen's types of glycogenosis.

Amylopectinosis (Andersen's Disease)

35. Andersen, D. H. Familial Cirrhosis of the Liver with Storage of Abnormal Glycogen. Lab. Invest. 5:11, 1956.
First case of amylopectinosis reported.

*36. Sidbury, J. B., Mason, J., Burns, W. B., Jr., Ruebner, B. H.. Type IV Glycogenosis. Report of a case Proven by Characterization of Glycogen and Studied at Necropsy. Bul. J. Hopkins Hospital 111:157, 1962.
The second case of amylopectinosis to be reported. Amylopectin demonstrated in liver and in red cells despite prolonged steroid therapy. Patient died of cirrhosis at age 4 years.

Muscle Phosphorylase Type (McArdle-Schmid-Pearson Disease)

37. McArdle, B. Myopathy Due to Defect in Muscle Glycogen Breakdown. Clin. Sc. 10:13, 1951.
First clinical description of what in retrospect was probably muscle phosphorylase defect.

38. Leloir, L. F., Olavarria, J. M., Goldemberg, S. H., and Carminatti, H. Biosynthesis of Glycogen from Uredine Diphosphate Glucose. Arch. Biochem. Biophys. 81:508, 1959.
Description of the UDP6 pathway in muscle.

39. Schmid, R. and Mahler, R. Chronic Progressive Myopathy with Myoglobinuria. Demonstration of a Glycogenolytic Defect in the Muscle. J.Clin. Invest. 38:2044, 1959.
Schmid, R., Robbins, P. W., Traut, R. R. Glycogen Synthesis in Muscle Lacking Phosphorylase. Proc. Nat. Acad. Sc. 45:1236, 1959.
Reports a 52 year old man with pain and weakness on slight exercise usually followed by myoglobinuria. Muscle phosphorylase was <1% of normal.

40. Schmid, R. and Hammaker, L. Hereditary Absence of Muscle Phosphorylase (McArdle's Syndrome). N. Eng. J. Med. 264:223, 1961.
Genetic study of family with McArdle's disease. Two of nine siblings of patient in Ref. 39 had disease. Three of 13 in second generation had McArdle's; therefore, probable autosomal recessive trait.

41. Pearson, C. M., Rimer, D. G. and Mommaerts, W.F.H.M. A Metabolic Myopathy due to Absence of Muscle Phosphorylase. Amer. J. Med. 30:502, 1961.
Mommaerts, W.F.H.M., Illingsworth, B., Pearson, C.M., Gullory, R.J. and Seraydarian, K. A Functional Disorder of Muscle Associated with the Absence of Phosphorylase. Proc. Nat. Acad. Sc. 45:791, 1959.
Two reports describe same 19 year old patient with muscle cramps, one episode of probable myoglobinuria on moderate exercise and absent muscle phosphorylase.

Hepatic Phosphorylase Type (Hers' Disease)

42. Hers, H. G. Études Enzymatiques sur Fragments Hépatiques: Application a la classification des Glycogénoses. Rev. Int. Hepat. 9:35, 1959.
Hers, H. G. Recent Developments in the Biochemistry of Glycogen Storage Disease and of Fructose Intolerance. Chem. Weekblacl. 57:437, 1961.
Presents 3 patients with hepatomegaly; increased liver glycogen and decreased but not absence of liver phosphorylase.

43. Leloir, L. F. and Goldemberg, S. H. Synthesis of Glycogen from Uridine Diphosphate Glucose in Liver J. Biol. Chem. 235:919, 1960.
UDP glucose pathway in liver.

44. Williams, H. and Field, J. B. Low Leukocyte Phosphorylase in Hepatic Phosphorylase Deficiency Glycogen Storage Disease. J. Clin. Invest. 40:1841, 1961.
Liver and leukocyte phosphorylase was depressed in 2 boys with hepatomegaly and elevated liver glycogen. Normal mother showed leukocyte phosphorylase depression.

45. Hulsman, W. C. Oei, T. L. and van Creveld, S. Phosphorylase Activity in Leucocytes from Patients with Glycogen Storage Disease. Lancet II:581, 1961
In four cases of hepatic form of glycogen storage (Hers') disease leukocyte phosphorylase is 1/4th normal. Sister of one and mother of two patients also had low leukocyte phosphorylase.

Studies Suggesting That Glycogen Storage is More Complex than Each Enzyme Defect Causing a Single Disease

46. Calderbank, A., Kent, P. W. Lorber, J., Manners, D. J. and Wright, A. Biochemical Investigation of a Case of Glycogen Storage Disease (von Gierke's). Biochem. J.74:223,1960.
In same family one sibling had von Gierke's disease and another sibling had debranching defect.

47. Perkoff, G. T., Parker, V.J., Hahn, R. F. The Effects of Glucagon in Three Forms of Glycogen Storage Disease. J. Clin Invest. 41:1099, 1962.
Report a patient with defect in both glucose-6-phosphatase and debranching enzyme. Glucagon therapy was of temporary benefit (3 months) only in two patients with glucose-6-phosphatase deficiency or in one with debranching defect, or in the one patient with combined defects.

48. Eberlein, W R. and Illingsworth, B. A. Heterogeneous Glycogen Storage Disease in Siblings and Favorable Response to Synthetic Androgen Administration. Am. J. Med. 33:20, 1962.
In two siblings male had glucose-6-phosphatase deficiency in liver and debranching enzyme defect in red blood cells. Sister had debranching of muscle liver and red blood cells. Androgen therapy caused marked clinical improvement, especially in male.

49. Lowe, C.U., Sokal, J. E., Mosovich, L.L., Sarcione, E. J. and Doroy, B. H. Studies on Liver Glycogen Storage Disease Effects of Glucagon and other Agents on Metabolic Pattern with Clinical Status. Am. J. Med. 33:4, 1962.
One patient had both glucose-6-phosphatase and phosphorylase defect. Results postprandial glucagon therapy were "encouraging" but could not predict effect on lactate and glucose on basis of lesion.

50. Editorial. A Confusion of Errors. Lancet 2:764, 1962.
Discussion of the apparent exceptions to the one gene-one enzyme hypothesis in glycogen storage diseases.

51. Anderson, C.M., Townley, M. D. and Freeman, M. Intestinal Sucrase and Isomaltase Deficiency in Two Siblings. Ped. 31:1003, 1963.
Intestinal debranching enzyme as well as surcrase (separate enzyme splitting sucrose to glucose and fructose) missing in each of two siblings. An example of two distinct enzyme deficiencies occurring in same individuals.