INVESTIGATIONS ON GLYCOGEN DISEASE

BY

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Under the title 'chronic hepatogenic hypoglycaemia in childhood' we described some time ago a number of investigations in a boy who had had a very large liver since birth. Clinically he gave the impression of adiposogenital dystrophy, and, in addition, he showed a very marked disturbance of carbohydrate metabolism. The predominant features of this disturbance were chronic hypoglycaemia in the fasting state, without the usual symptoms, and accompanied by ketosis; little or no change in the blood-sugar value after subcutaneous injection of adrenalin, and hypersensitiveness to small quantities of insulin. As a cause of this anomalous disturbance we conceived a continuation of the foetal condition, and we sought in faulty glycogenolysis an explanation of the condition. Thus in our boy the ketosis and the absence of hyperglycaemic response to adrenalin might not depend upon a poor glycogen content of the liver.

We found support for our ideas especially in the publications of von Gierke and Schönheimer. We thought we had to deal in our boy with a case of hepatomegalia glycogenica as described by von Gierke, and that the disturbances in metabolism in our case were characteristic for this form of liver hypertrophy. The features of this hypertrophy were the accumulation of glycogen, which during life and after death could be mobilized only with difficulty. Since then the interest in 'glycogen disease' has greatly increased and different authors have published definite cases of 'hepatomegalia glycogenica,' which have been studied clinically. The deviations in metabolism found by these authors as a whole agree with those found in our case. In our opinion our case is therefore one of hepatomegalia glycogenica and in this we are supported by the recent findings of other investigators. It is important to note that this interesting glycogen disease must be regarded as a general disease of metabolism, in which the glycogen can only be mobilized with difficulty, and may accumulate in various organs, not only in the liver. In this way it may give rise to hypertrophy of different organs. This accumulation of glycogen plays a big rôle in the occurrence of a number of congenital deviations and in those arising shortly after birth. Thus, it is a disturbance which merits the consideration of paediatricians, and the study of this disturbance will increase our insight into several diseases of childhood. Further, glycogen disease and
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the conduct of the glycogen in this disease have undoubtedly a very interesting and more general physiological and pathological significance. Elsewhere\textsuperscript{13, 14} we have written more extensively upon the significance of glycogen in the occurrence of hypertrophy of other organs than the liver (heart, kidneys, pylorus).

We have been able to continue our observations in this patient with the large liver and to extend our researches during last year. Further, a second child, which presented almost the same morbid picture with analogous deviations in metabolism, has come under our care. We have attempted, as before, to investigate the disturbance of metabolism in this disease, and to make more exact its differential diagnosis from other chronic liver diseases, especially from the cirrhoses.

B., a girl, the second case, now six years old, was a full-term child, delivered spontaneously. Throughout her pregnancy the mother remained well. The child's weight at birth was just over 7 lb. She was breast-fed until the age of 10 months. Her weight when one year old was about 21 lb. Throughout this time the physical condition remained good and there was no evidence of rickets. The mental development of the child was normal. Though not clinically established there is much evidence to suggest that the child at birth had already a large liver. In a photograph, taken at the age of 6 months, the abnormally large circumference of the abdomen can be distinctly seen, and before the end of the first year the presence of an abnormally large liver had been established with certainty. We know that during the first year of life no peculiarities occurred.

After the first year of life this child, just as in the case of our first patient, had periodic attacks of persistent vomiting in the morning and showed also a special preference for bread. When the mother came to us with the child in January, 1932, there were no other complaints apart from this nausea and vomiting. The child was hindered in her movements by the enormous abdomen. The child was alert. The mental development was normal and she went to a preparatory school. She had a good appetite, preferred bread, had no complaints of the abdomen, and no attacks of fever.

Father normal. Mother was 37 years when the child was born, this being her 7th pregnancy and the first child of her second marriage. She had had one abortion, once a still-born twin; one child died at the age of one year from bronchopneumonia following measles. The other children are normal; no known enlargement of the liver in the family. Of the medical condition of the first husband little is known, except that he was a drunkard. The Wassermann reaction (Jan., 1932) in the mother was negative. Since the birth of the girl the mother has had no further pregnancies. No family history of tuberculosis.

On examination (Jan., 1932) the girl, nearly 5 years old, weighed 35\textperthousand lb., and was only 38 in. in height. She was well nourished with normal subcutaneous fat, and no suggestion of adiposity. No icterus. Colour of the skin was somewhat dark but showed no pigmentation of skin or mucous membranes. No abnormal growth of hair. Rather marked dental caries. The neck was short, and on both sides were numerous small glands. The abdomen was protuberant. Heart, blood-pressure and lungs were normal.

The abdomen was greatly distended as a whole, and on the upper part of the wall of the abdomen a fine net of veins was seen; no caput medusae. The distension of the abdomen was caused by a very large liver, which occupied nearly the whole right and the greater part of the left half of the abdomen. On the right side it was almost impossible to place the hand between the liver and the edge of the pelvis. The left lobe of the liver could be felt from the level of the umbilicus, slanting upwards and disappearing under the costal arch at about the axillary line. Just at the umbilicus an incisura could be felt. The liver was of firm consistence and felt smooth; its
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edge was sharp. No pain on palpation of the abdomen. No signs of free fluid. The greatest circumference of the chest was 21 in. and of the abdomen 25 in. The spleen could with difficulty be felt; kidneys not palpable. External genitals normal. Reflexes normal, muscular system normal; the legs slim. The child was not easily exhausted by exercise.

The child was intellectually normal. She complained of no abdominal symptoms, and showed no clubbing of the fingers.

The urine in fasting condition contained no albumen or sugar, and showed a weakly positive reaction for urobilin, and strongly positive tests for acetone and diacetic acid. Bile absent. Specific gravity normal. Nothing abnormal in the sediment. Stool: normal colour and consistency; no worms or ova; on a mixed diet the fat-content was not increased. The Pirquet, Wassermann and Weinberg reactions were all negative. Temperature normal.

Examination of the blood showed a leucocyte count of 12,700 with 5 per cent. eosinophils and a moderate relative lymphocytosis; no anaemia; platelets normal. Throughout the last year the blood was investigated repeatedly with similar results; except that the leucocyte count was normal and the eosinophilia less. A distinct leucopenia, as found in the boy, was not found.

X-ray investigation: no enlargement of the heart; no signs of active rickets; no apparent abnormalities of the extremities with the exception of several small transverse lines in the bones of the lower extremities as a sign of irregular growth; some delayed ossification, in both wrists only three of the small bones were ossified. Sella turcica normal. Kidneys normal; no abnormalities in the region of the adrenal glands. Bones of the skull were normal.

Electrocardiogram normal. Basal metabolism slightly increased (two determinations, +19 and +27 per cent. At the second determination the child was not quiet).

The girl therefore showed a greatly enlarged liver without demonstrable hypertrophy of other organs, but with definitely delayed growth. Marked ketosis and slight urobilinuria were present. No signs of an endocrine disturbance were found and especially no marked adiposity as was found in our boy.
Blood sugar.—In the fasting condition there was a combination of hypoglycaemia and ketosis: in the capillary blood the blood sugar at different determinations ranged between 0.046 and 0.059 per cent.; in the venous blood between 0.05 and 0.06 per cent. (Hagedorn and Jensen).

In our boy the fasting blood-sugar values now show a tendency to rise (in the capillary blood 0.057–0.073 per cent.). In the girl all clinical symptoms of the so-called hypoglycaemic complex as occurs in hyper-insulinism were absent.

In addition, after 25 gm. of glucose the girl showed a biphasic blood-sugar curve. The blood sugar remained increased for a long time and had not returned to the fasting level after 2½ hours, which in itself is strongly against hyper-insulinism. The maximal elevation was only from 0.058 to 0.112 per cent.; no glucosuria occurred.

After 20 gm. of fructose the fasting blood sugar rose from 0.056 to a maximum of 0.088 per cent., i.e., a little higher than may occur normally (30 mgm. per cent.), but the increase lasted for more than two hours. The urine contained no reducing substances, and the ketosis existing in the fasting condition decreased very much after giving fructose.

After 25 gm. of galactose no sugar was excreted in the urine.

The elevation of the respiratory quotient after giving 20 gm. of glucose was investigated; in one hour the quotient rose above 1, but the girl had not remained quiet.

Adrenalin test.—After subcutaneous injection of 0.5 mgm. of adrenalin the girl showed only a very slight elevation of the blood sugar: in the first test from 0.054 to 0.07 per cent., in the second test from 0.051 to 0.066 per cent. But a markedly increased excretion of ketones after the adrenalin injection was noticed. In our boy, although his fasting blood sugar is distinctly higher than formerly, a significant rise of blood sugar after injection of adrenalin does not take place: in one test recently performed a rise from 0.069 to 0.072 per cent. occurred within two hours after the injection.

In view of the adrenalin effect our idea of the cause of the blood-sugar elevation after adrenalin injection must be reconsidered. The Coris have demonstrated in different ways that the blood-sugar elevation which normally occurs after adrenalin injection, is only partly caused by mobilization of liver glycogen and this only in so far as the primary elevation is concerned. In speculating as to the existence of a glycogen depot in the liver which can be mobilized, stress must therefore, a priori, be laid upon the non-appearance of this initial elevation.

In both our patients, however, it appeared that the adrenalin effect was also abnormal in so far as the rise of the lactic acid content of the blood, which normally accompanies adrenalin hyperglycaemia and which is related to an increased splitting of muscle glycogen, was only very small.

In this connection we wish to point out the disturbance of glycogen splitting and of lactic acid formation in muscle, which occurs after extirpation of the adrenals and is accompanied by an increased consumption of creatine phosphoric acid. It appeared that creatine was present in the urine of both our children, but in an amount normal for their age.
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In still another way the adrenalin effect in both our children appeared to be deviating from normal. When in normal men subcutaneous injection of adrenalin is combined with oral administration of glucose in an amount normally used for tolerance tests, then the elevation of the blood sugar is for the most part much more marked than after adrenalin injection or glucose ingestion alone (Burkens). This is apparently a consequence of the second adrenalin effect, that is, a decrease of sugar consumption in the muscles by which the extra glucose given orally causes a higher elevation of the blood sugar. In both our patients such a test has been done once. In both cases the elevation of the blood sugar after adrenalin injection together with glucose ingestion, was only slightly greater than after glucose ingestion alone.

From investigation of the protein spectrum of the blood serum it appeared that the very important increase of the globulin content of the serum which is present in the majority of chronic parenchymatous liver affections\textsuperscript{16} was absent in both our patients (compare the two control cases in Table 1).

\begin{table}
\centering
\caption{Protein spectrum of blood plasma.}
\begin{tabular}{|l|c|c|c|c|}
\hline
\ & Normal & Glycogen liver & Hepatic cirrh. 12 years & Gaucher's dis. 13 years \\
\hline
\ & Pat. B. & Pat. E. & & \\
\hline
Total protein.. & 6.5 - 8 & 8.34 & 7.63 & 9.02 & 91.4 \\
Albunen.. & 4.5 - 5.5 & 5.26 & 4.66 & 5.02 & 4.2 & 4.11 \\
Globulin.. & 1.8 - 2.4 & 2.69 & 2.52 & 2.09 & 4.28 & 4.8 \\
Fibrinogen.. & 0.25 - 0.38 & 0.39 & 0.65 & & 0.54 & 0.24 \\
\hline
\end{tabular}
\end{table}

Next with the serum of both patients we performed the flocculation test which according to modern investigations is always positive in chronic parenchymatous liver affections (the so-called Takata-Ara reaction)\textsuperscript{17}. In our boy E. the test was negative, in the girl B. it was only weakly positive.

Corresponding to the protein spectrum of the serum the sedimentation-rate of the erythrocytes of both our patients in the defibrinated blood as well as in the non-defibrinated blood was normal.

Certain determinations of different constituents of blood and blood serum have also been made in both our patients. Table 2 gives a survey of the results. From this it appears that in the girl as well as in the boy there was a marked elevation of the cholesterol content. In both our patients the relation between free cholesterol and cholesterol esters, a relation which in liver diseases is often changed, was normal. There was no decrease of cholesterol esters. In both our patients with hypoglycaemia the non-sugar reducing fraction and glutathion content (Groen) were normal. It further appeared that the lipolytic activity of the serum of both our patients was
also normal. In addition, a choline-, and an atoxyl-resistant lipase (as may be present in the serum in parenchymatous liver and pancreas affections) were absent from the serum.

**TABLE 2.**

**SOM'EST C0NSTITUENTS OF BLOOD SERUM.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl in total blood</td>
<td>0.29</td>
<td>0.24</td>
<td>0.27 - 0.30</td>
</tr>
<tr>
<td>Cl in serum</td>
<td>0.38</td>
<td>0.37</td>
<td>0.35 - 0.40</td>
</tr>
<tr>
<td>Ca in serum</td>
<td>12.56 mgm.</td>
<td>10.70 mgm.</td>
<td>7.8 - 11.95 mgm.</td>
</tr>
<tr>
<td>Ca in serum ultrafiltrates</td>
<td>8.376 mgm.</td>
<td>—</td>
<td>4.86 - 6.41 mgm.</td>
</tr>
<tr>
<td>Mg in serum</td>
<td>2.503 mgm.</td>
<td>—</td>
<td>1.5 - 3 mgm.</td>
</tr>
<tr>
<td>Mg in serum ultrafiltrates</td>
<td>1.695 mgm.</td>
<td>—</td>
<td>2 mgm.</td>
</tr>
<tr>
<td>Inorganic P in blood</td>
<td>4 - 5 mgm.</td>
<td>3.8 mgm.</td>
<td>2.5 - 4 mgm.</td>
</tr>
<tr>
<td>Cholesterol in blood</td>
<td>200 - 263 mgm.</td>
<td>210 - 221 mgm.</td>
<td>160 - 180 mgm.</td>
</tr>
<tr>
<td>Free cholesterol</td>
<td>33.5</td>
<td>41</td>
<td>30 - 40</td>
</tr>
<tr>
<td>Cholesterol esters</td>
<td>64.5</td>
<td>59</td>
<td>60 - 70</td>
</tr>
<tr>
<td>Non-sugar reducing fraction</td>
<td>27.5 mgm.</td>
<td>28 mgm.</td>
<td>22 - 28 mgm.</td>
</tr>
<tr>
<td>Glutathion</td>
<td>34 mgm.</td>
<td>34 mgm.</td>
<td>25 - 40 mgm.</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>—</td>
<td>1.08 units</td>
<td></td>
</tr>
</tbody>
</table>

**GLYCOGEN METABOLISM.**—During the last year we studied in different ways the glycogen metabolism of both our patients; firstly, the so-called initial insulin hyperglycaemia which when present would prove the existence of a glycogen depot. The effect is not given by pure insulin preparations18. Using an insulin preparation of Burroughs Wellcome & Co., which in animal experiments was proved to produce an initial rise in blood sugar, we found no such effect in our girl (Table 3). The absence of this effect in

**TABLE 3.**

**INVESTIGATION AFTER THE SO-CALLED INSULIN HYPERGLYCAEMIA.**

<table>
<thead>
<tr>
<th></th>
<th>Blood sugar in mgm. per cent.</th>
<th>Maximal elevation per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After 5</td>
</tr>
<tr>
<td>Normal</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>Patient B</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Severe jaundice</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Recovered jaundice</td>
<td>79</td>
<td>97</td>
</tr>
</tbody>
</table>
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her case is, as we now know, not due to an insufficient glycogen depot, but
to a glycogen supply which can be mobilised only with difficulty.

The glycolysis of the blood of the girl B. was normal, as was that of
the boy E. The same holds true for the influence exerted by insulin in
vitro on the oxidative glucose fermentation by erythrocytes19 of our patients.
For this investigation we made use of a pure insulin preparation kindly
provided by Prof. Laqueur.

The quantity of diastase in blood and urine of both patients proved to
be normal. An increased diastase excretion in the urine, as found by some
investigators, was not found by us. Again, the so-called diastase-fortifying
action of the blood serum20, by which is meant the smallest quantity of
serum which in vitro exercises a fortifying action on a pancreatic amylase,
was normal in both our patients.

Special attention was paid to the glycogen in the blood of our patients.
Could this glycogen be split? Little is known up to the present regarding
the glycogen of the blood. According to Gabbe21, in the normal blood the
glycogen should, even on keeping for several hours at 37° C., decrease only
very slightly, notwithstanding the presence of a glycogenolytic ferment.
Thus the blood glycogen should in this stability resemble the glycogen
present during foetal life, and differ in this respect from that present in liver
and muscle, corresponding to that existing in liver and different organs in
glycogen disease.

With our method, which could be regarded as a micro-modification of
Pfüger's method, we had obtained for the glycogen content of the blood of
the boy E. some results which could be called distinctly high. Since then
we have paid special attention to the method of determination of blood
glycogen and we have elaborated a method which certainly will be of
importance in the future. Our method is as follows:—

DETERMINATION OF GLYCOGEN IN 1 C.C. OF BLOOD.—1 c.c. of blood is haemolysed by
adding 1 c.c. of distilled water in a wide Pyrex centrifuge tube with a ground glass
stopper. Two cubic centimetres of 60 per cent. KOH are added and the closed tube is
heated in a boiling water bath for 15-20 minutes and carefully shaken from time to
time. After cooling, 8 c.c. of distilled water and 16 c.c. of absolute alcohol or 96 per
cent. alcohol are added and the contents of the tube carefully mixed. The precipitated
glycogen is allowed to settle overnight. After centrifuging, the precipitate is washed
at least twice with 66 per cent. alcohol. The glycogen is determined as glucose by
hydrolysing with 4 c.c. 2.2 per cent. HCl for two hours, after evaporation of the
remaining alcohol. The material is now neutralised with 2N. NaOH using phenol
red (one drop) as indicator. The glucose is determined after the method of
Hagedorn and Jensen. The whole determination is thus carried out in the same tube.

In our earlier investigations we did not haemolysate the blood and this is probably
the reason why our double determinations did not always correspond. The change
in the time of boiling with KOH from two hours to 15-20 minutes we obtained from
the recent publication of Good, Kramer and Somogyi22. For the rest we still follow
the method described above with excellent results; the method was tested using
blood to which known amounts of glycogen had been added. We found a maximum
error of 10 per cent.

Since we have used the above method for the determination of glycogen
we have constantly found in the fasting blood of both our patients values
which we look upon as high, no leucocytosis being present which could cause
this elevation. The results of a series of determinations during the past 14 months were as follows:—Glycogen content of blood (as mgm. glucose per 100 c.c. of blood): Patient B. 23-75, 23, 20, 19-25, 21-25, 18-75, 21-85, 21, mean value, 21-04; Patient E. 26, 25, 23-05, 27-5, 22-9, 26-62, 26-25, 24, 28, 25, mean value, 25-43. Next (Table 4) we give the results obtained in a

TABLE 4.

GLYCOGEN CONTENT OF THE BLOOD.

(expressed as glucose in mgm. per cent.)

35 determinations in children:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Glycogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.</td>
<td>5-10, 10-15, 15-17, 17-20, 20-22</td>
</tr>
</tbody>
</table>

Blood from umbilical cord:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Glycogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.</td>
<td>5-10, 10-15, 15-17, 17-20, 20-22</td>
</tr>
</tbody>
</table>

Determinations in adults:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Glycogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison's disease</td>
<td>7-06, 7-38</td>
</tr>
<tr>
<td>Lues hepatitis</td>
<td>12-12, 12-62</td>
</tr>
<tr>
<td>Cirrhosis hepatitis</td>
<td>16-75, 17-4</td>
</tr>
<tr>
<td>Congested liver</td>
<td>26-1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>18</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>12-45</td>
</tr>
</tbody>
</table>

Examples

<table>
<thead>
<tr>
<th>Condition</th>
<th>Glycogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cong. pyloric stenosis</td>
<td>10-2</td>
</tr>
<tr>
<td>Premature infants</td>
<td>13-17</td>
</tr>
<tr>
<td>Hypertrophy of the heart in</td>
<td>15-75, 15-10</td>
</tr>
<tr>
<td>patent interventricular septum</td>
<td></td>
</tr>
<tr>
<td>Cyclic vomiting</td>
<td>16-13</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>18-75</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>12-75</td>
</tr>
<tr>
<td>Myelogenous leukaemia</td>
<td>71</td>
</tr>
<tr>
<td>(150,000 white cells)</td>
<td>48-5</td>
</tr>
<tr>
<td>Renal rickets</td>
<td>6-35</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>13-5</td>
</tr>
</tbody>
</table>

number of children some of whom were healthy, the others suffering from varying diseases; a number of determinations also were made in blood from the umbilical cord and are noted in this table. In children under 12 years of age, as is reported in the table, with the exception of our patients, we found by our method only one glycogen value above 20 mgm. per cent., and that in a premature child; as a rule the value was much lower. We also once found a value above 20 mgm. per cent. in a child with miliary tuberculosis. On these grounds we think we are justified provisionally in saying that the elevation of the glycogen content of the blood is of some diagnostic significance in the diagnosis of hepatomegaly glycogenica. We say ' provisionally ' because blood of infants with other forms of liver
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hypertrophy was not available. We were able to examine the blood of adults with marked liver hypertrophy. A priori we are not justified in comparing these values with those obtained in children with liver hypertrophy and especially with those obtained in our patients, because the glycogen metabolism in childhood occupies a separate place, as has been shown clinically and experimentally. In adults with liver hypertrophy values as found in our children also occur. When the number of leucocytes is greatly increased, this in itself may be the explanation of a marked elevation of the glycogen content. In an adult female patient with myeloid leukaemia and a large liver (150,000 leucocytes) we found a very high glycogen content of the blood in two determinations, 48·5 and 71 mgm. per cent., expressed as glucose.

Incidentally it may be noticed that according to the table the glycogen increase did not occur in two cases of pyloric spasm, an affection in which an accumulation of glycogen must be considered as a possible cause of the hypertrophy. Further, we recently found in the case of a baby where at the autopsy histological and histo-chemical, and later on chemical investigation revealed an accumulation of glycogen in the heart muscle (idiopathic hypertrophy of the heart, vide infra), that the blood obtained after death contained 18 mgm. per cent. of glycogen; a value which in our experience is at the highest limit of the normal values. The fluid with which the organs were bathed at autopsy contained however already 87 mgm. per cent. of glycogen. It is improbable that cases of glycogen disease, where hypertrophy does not primarily concern the liver, should show analogous deviations in metabolism to our patients. Little can at present time be said about the glycogen of the blood in such cases.

In Table 4 we give some results obtained in adults suffering from diseases in which the carbohydrate metabolism was specially concerned.

As to the splitting of the glycogen of the blood we agree with Gabbe in judging that this glycogen can be split only with difficulty. Blood was collected with aseptic precaution and received in sterile tubes. After incubation for 1½ hours at 37° C. the blood of our patients showed no splitting of its glycogen. In normal children the blood glycogen not uncommonly shows marked splitting in the same time. In keeping this normal blood for 48 hours at 37° C. we constantly found that a definite but varying decrease of the glycogen content could be demonstrated and in this we differ from Gabbe. In our patients the decrease of the glycogen content of the blood under the same conditions which are so favourable for splitting, proved to be smaller than the mean decrease in the control patients and it scarcely agreed with the lowest values found in control children (Table 5).

Further, we found that glycogen added to serum of our patients and to serum of control patients was split by both in the same degree and in the same time.

Our next step was to find out whether by mixing the blood of our patients with that of control children and keeping it for 48 hours at 37° C.
the splitting of the blood glycogen of our patients could be accelerated. Increased glycogenolysis was not constantly found, however, so that provisionally we are not justified in concluding, as we thought at first, that

**TABLE 5.**
**GLYCOGEN VALUES OF BLOOD DETERMINED DIRECTLY AND AFTER INCUBATION FOR 48 HOURS AT 37° C. EXPRESSED IN MOM. GLUCOSE PER 100 C.C. OF BLOOD.**

<table>
<thead>
<tr>
<th>Control patients</th>
<th>Immediate</th>
<th>After 48 hours at 37° C.</th>
<th>Decrease in per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ... ...</td>
<td>15-75</td>
<td>10-5</td>
<td>33-33</td>
</tr>
<tr>
<td>2 ... ...</td>
<td>13-75</td>
<td>10-25</td>
<td>25-46</td>
</tr>
<tr>
<td>3 ... ...</td>
<td>16-75</td>
<td>9-6</td>
<td>42-68</td>
</tr>
<tr>
<td>4 ... ...</td>
<td>17-4</td>
<td>12-8</td>
<td>26-43</td>
</tr>
<tr>
<td>5 ... ...</td>
<td>15-75</td>
<td>6-5</td>
<td>58-73</td>
</tr>
<tr>
<td>6 ... ...</td>
<td>11-75</td>
<td>5-5</td>
<td>53-2</td>
</tr>
<tr>
<td>7 ... ...</td>
<td>10</td>
<td>5-5</td>
<td>18-3</td>
</tr>
<tr>
<td>8 ... ...</td>
<td>16-62</td>
<td>7-375</td>
<td>52-79</td>
</tr>
<tr>
<td>9 ... ...</td>
<td>12-12</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>10 ... ...</td>
<td>18</td>
<td>13-75</td>
<td>23-6</td>
</tr>
<tr>
<td>11 ... ...</td>
<td>12-62</td>
<td>8</td>
<td>36-6</td>
</tr>
<tr>
<td><strong>mean decre.</strong></td>
<td></td>
<td></td>
<td>39-26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient E</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ... ...</td>
<td>24</td>
<td>19-25</td>
<td>20</td>
</tr>
<tr>
<td>2 ... ...</td>
<td>28</td>
<td>24-25</td>
<td>13-4</td>
</tr>
<tr>
<td>3 ... ...</td>
<td>25</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td><strong>mean decre.</strong></td>
<td></td>
<td></td>
<td>19-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient B</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ... ...</td>
<td>21-25</td>
<td>16-5</td>
<td>22-25</td>
</tr>
<tr>
<td>2 ... ...</td>
<td>23-1</td>
<td>18-75</td>
<td>19</td>
</tr>
<tr>
<td><strong>mean decre.</strong></td>
<td></td>
<td></td>
<td>20-62</td>
</tr>
</tbody>
</table>

there exists in normal blood a substance which favours the splitting of the blood glycogen of our patients.

In summarizing (Table 6) the above results of the clinico-chemical investigation, we found in both cases, in addition to our former findings in our boy:

1. A combination of hypoglycaemia and ketosis in the fasting condition.
2. An abnormal adrenalin effect, expressing itself by:
   a. Absence of a distinct elevation of the blood sugar.
   b. A marked increase of the ketosis.
   c. Only a small elevation of the lactic acid content of the blood.
3. An abnormal blood sugar curve after ingestion of glucose, unaccompanied by glycosuria.
4. No diminution in tolerance to galactose and fructose.
5. Absence of the so-called initial insulin hyperglycaemia.
6. a. Normal values for the diastase activity of blood and urine.
   b. Normal diastase activating effect of the serum.
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7. Increased glycogen content of the blood, which could not be explained by leucocytosis.
9. Decreased glycogenolysis of the blood glycogen on incubation for two days at 37°C, compared with control cases.
10. Normal protein spectrum, especially no increase of the globulin content.
11. Hypercholesterolaemia with normal relation between free cholesterol and cholesterol esters.

**TABLE 6.**

**SURVEY OF THE MOST IMPORTANT SYMPTOMS IN TWO CASES OF GLYCOGEN LIVER.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pat. E.</th>
<th>Pat. B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Infantilism</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Adiposity</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Psychical development</td>
<td>...</td>
<td>normal</td>
</tr>
<tr>
<td>Appearance of endocrine disturbance</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypoglycaemia plus ketosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blood sugar curve after glucose</td>
<td>abnormal</td>
<td>abnormal</td>
</tr>
<tr>
<td>Adrenalin effect</td>
<td>blood sugar</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>lactic acid</td>
<td>&quot;</td>
</tr>
<tr>
<td>Insulin effect, so-called insulin hyperglycaemia</td>
<td>...</td>
<td>absent</td>
</tr>
<tr>
<td>Sensitivity to insulin</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Galactose test</td>
<td>...</td>
<td>normal</td>
</tr>
<tr>
<td>Fructose test</td>
<td>...</td>
<td>&quot;</td>
</tr>
<tr>
<td>Glycolysis of blood</td>
<td>...</td>
<td>&quot;</td>
</tr>
<tr>
<td>Glycogen of blood</td>
<td>...</td>
<td>increased</td>
</tr>
<tr>
<td>Glycogen of serum ultrafiltrate</td>
<td>...</td>
<td>normal</td>
</tr>
<tr>
<td>Glycogenolysis of blood glycogen</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>Splitting of glycogen added to serum</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>D&amp;astatic power of blood</td>
<td>...</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>urine</td>
<td>&quot;</td>
</tr>
<tr>
<td>Water metabolism</td>
<td>...</td>
<td>disturbed</td>
</tr>
<tr>
<td>Cholesterol of blood</td>
<td>...</td>
<td>increased</td>
</tr>
<tr>
<td>Proportion of free cholesterol to esters</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Protein spectrum of serum</td>
<td>...</td>
<td>&quot;</td>
</tr>
<tr>
<td>Urobinuria</td>
<td>...</td>
<td>&quot;</td>
</tr>
<tr>
<td>Basal metabolism</td>
<td>...</td>
<td>slightly increased</td>
</tr>
<tr>
<td>Heart (size, E.C.G.)</td>
<td>...</td>
<td>normal</td>
</tr>
<tr>
<td>Kidney (size)</td>
<td>...</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

We did not think we were justified when we know already so much about the metabolism of our children, in doing a laparotomy and biopsy of the liver in the girl B., as has been done elsewhere (Beumer and Loeschke, Schall). In epithelial cells (mucous membrane of the cheek, cells of the mucous membrane of the kidney in the sediment of freshly voided urine) we could demonstrate no glycogen in the girl B. by the staining method of Best. Nor could we find an increased amount of glycogen in the urine. In the leucocytes from a small granuloma at the root of a molar we found much glycogen (de Vries). This in itself certainly has no great significance, but the absence of glycogen in this tissue would not have been in keeping with the morbid picture.
About the cause of the difficulty in the splitting of the glycogen in glycogen disease nothing can be said with certainty. Blood and urine of our patients showed a normal diastatic activity (according to some investigators the urine sometimes showed an increased activity); the diastase in the liver is probably in normal quantity. How is the glycogen in such a particular way protected in this disease? Does it form a compound with protein or have we to deal here with another modification of glycogen without the question of another chemical polysaccharide? Or must we seek the solution in the hormonal direction?

The conception of a glycogen which, for example, was difficult to split owing to an abnormal binding of protein (a conception mentioned by Unshelm), has been investigated by us with the help of W. M. Bendien. We determined the glycogen content of the blood serum of our patients and of that of some control children and then of the ultrafiltrate of these blood sera prepared in different ways. It now appeared that a part of the serum glycogen is always present in the protein-free ultrafiltrate. The values obtained for this ultrafiltrable part of the serum glycogen varied between 2½ and 4 mgm. per cent., with very different values for the serum glycogen. In both our patients the quantity of this ultrafiltrable part showed no departure from normal. When the protein content of the ultrafiltrate was increased, the corresponding glycogen content also increased and approximately in proportion to the protein content. We are still investigating whether the non-ultrafiltrable glycogen in the serum is indeed bound to the protein, and whether there are still further differences in this connection between these patients and other normal children. Up to the present we have found no evidence for the existence of a particular combination of the glycogen in our patients.

As to the conception of the glycogen disease as a hormonal disturbance we would note the following. The whole picture of glycogen disease, whether the liver alone is concerned, or whether in addition to this there exists hypertrophy of other organs, cannot be correlated with any known disturbance of internal secretion. We have been able to exclude a hyperinsulinism for different reasons. Also pathological examination of children who showed some hypertrophy of organs by accumulation of glycogen, did not give absolute indications in this respect. Perhaps an exception is provided by the first case of von Gierke, where atrophic adrenals were found, and perhaps also by the patient lately described by Bellingham Smith and O'Flynn, who showed marked pigmentation and abnormal growth of hair.

On the other hand, our conceptions about glycogen splitting in liver and muscles have undergone some fundamental changes by recent investigations. Firstly it appears that there exists a nervous influence on liver glycogen, which can express itself otherwise than through adrenalin and insulin. On the basis of these findings MacLeod even speculated as to the existence of two forms of glycogen in the liver, having a different functional behaviour. Further, we must point to the results of recent researches on the influence of the hormone of the adrenal cortex and of the anterior lobe of the pituitary upon carbohydrate metabolism.
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The essentials of glycogen disease cannot up to the present be wholly explained by these new facts. That in future we must reckon seriously with hormonal factors, may appear from the following example. One of the recent investigators, Viale, who looks upon the adrenal as a regulator of the carbohydrate metabolism, found that after extirpation of the adrenals the muscle glycogen after death did not disappear or it disappeared only slowly—even after incubation at 37°C. for several hours—i.e., this glycogen showed a property which we find in glycogen disease. The factors responsible for this change are still obscure.

Our first patient E. showed some clinical symptoms of a disturbance in the function of the hypophysis; these were absent in the second patient B. Neither child showed any abnormality of the chloride metabolism. The reaction of Aschheim-Zondek, performed upon the urine of both patients (Ivens) proved to be negative.

If we accept a hormonal cause for the occurrence of accumulation of glycogen which can be mobilized with difficulty, one asks oneself whether this factor may not always play a rôle in an early period of life. From many experimental observations we know that glycogen occurring in embryonic life and also shortly after birth behaves functionally differently from that in adults, but similarly to that in glycogen disease. We have already put forward the hypothesis, on the ground of an extensive examination of premature children, that in our first patient there might be the possibility of the persistence of a foetal condition. It has to be accepted that the factors which during foetal growth influence the local accumulation and the fermentative breakdown of glycogen in organs and under certain circumstances also in later life keep their function and in this way cause a marked hypertrophy by accumulation of glycogen in one or more organs.

An enlargement of the liver by accumulation of glycogen accompanied by hypoglycaemia may be caused experimentally by a certain diet (high carbohydrate with much protein), as has been demonstrated by Schöndorff and Junkersdorff. The latter found that this may succeed most easily in young animals. His conception that these observations must be considered seriously in explaining glycogen disease in man must provisionally, in our opinion, be denied. In the described cases of glycogen disease and in our patients nothing is known of a particular diet which preceded the onset of glycogen liver. For the most part we had to deal with a congenital abnormality. Further, it is highly questionable whether the glycogen which is accumulated in the liver and also in other organs under these experimental circumstances shows the peculiarities of the glycogen in glycogen disease, which during life and after death can be split only with difficulty.

Further clinical and clinical-chemical study of both our patients revealed the following facts. In our girl at the end of May, 1933, the height was 40 inches, i.e., an increase of 3 inches since January, 1932; during the same time her weight increased only from 35 1/2 to 39 1/2 pounds. The maximum abdominal circumference increased only 0-2 in. The bones of the wrist had developed to a greater extent during this time.

In our boy the height at the end of 1931 was 55 inches; in June, 1933, it was 57 inches. During the same time his weight increased from 75 to 95
pounds. He thus gives the impression of corpulence. It is important to state now, at the age of 12 years, nearly all his teeth are still milk teeth. The general condition of both patients is excellent.

As in the case of our boy, we prescribed for the girl a mixed diet rich in carbohydrates, with vegetables and fruit juice and very little fat. In the girl we are again and again impressed by her extraordinary preference for bread. Attacks of severe vomiting, which formerly occurred, occur no longer. In fasting condition, however, the urine always contains acetone and often also diabetic acid.

During last year we paid special attention to the ketosis in both our patients. In these cases of chronic ketosis were products of \( \omega \)-oxygenation of the fatty acids present in addition to the products of \( \beta \)-oxygenation as was discovered by Verkade\(^2\) and his co-workers? The urine of our patients, containing ketone bodies, was investigated for products of this oxygenation by Dr. Elzas in Rotterdam with negative results.

Could the ketosis of our patients be influenced by oral administration of choline? This question is of importance in view of the recent investigations of C. H. Best\(^3\) and his collaborators. From these it appears that a fatty degeneration or a superfluous fat depot in the liver may be prevented experimentally or much decreased by oral administration of choline; the glycogen content of the liver under these experimental conditions is not influenced. These results have been applied already to patients suffering from diabetes mellitus with severe ketosis. In cases of glycogen disease which came to autopsy there has sometimes been found in addition to the very large amounts of glycogen in the liver, much fat (e.g., in the two cases described by von Gierke). What was the effect of the choline on the ketosis and other symptoms in our patients? We obtained the definite impression that during the time that choline\(^*\) was used from October, 1932, to March, 1933, beginning with doses of 30 mgm. and slowly increasing to 600 mgm. daily, the mean excretion of ketones in both our patients was much lower than before. However, no influence was noted upon the fasting blood sugar, the glycogen content of the blood and the cholesterol content. After stopping the administration of choline the excretion of acetone remained minimal in our boy; even with the most sensitive methods often no acetone at all could be demonstrated in the fasting urine. In the girl the fasting urine usually contains more total acetone and \( \beta \)-oxybutric acid now than it did during the choline treatment.

The girl for many weeks was given small amounts of dried thyroid; no influence upon the metabolism was noted.

As compared with former examinations the most striking changes in our boy are the decrease of the ketosis, which has nearly disappeared, the marked elevation in the fasting blood sugar in the capillary blood already mentioned and the growth. The other abnormalities in his metabolism are present as before. There is still definite leucopenia, a count in June, 1933, showing 4,900 leucocytes. We think that the dimensions of his liver remain the same. After giving extra sugar the urine never contains any sugar.

\* Our thanks are due to M. Guggenheim in Basle and also to G. H. Nijhoff, apothecary at Amsterdam (Wilhelmina-Gasthuis) for procuring us the needed choline.
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Differential diagnosis.

Are the symptoms of hepatomegaly glycogenica as found in both our patients characteristic for this disease? This question is of great importance in the differential diagnosis from other chronic liver diseases and to a certain extent from those of other organs (e.g., adrenal tumours and kidney tumours). It is also important, therefore, in considering whether in a certain case a laparotomy should be done. Our own experience and recent publications about glycogen disease with marked hypertrophy of the liver give us ground to answer this question provisionally in the affirmative. In hepatomegaly glycogenica there exists a series of symptoms (Table 6) which have never been observed in other chronic liver affections, at least not in this combination, viz., very marked congenital enlargement of the liver, or the same enlargement coming on shortly after birth, an enlargement in which the surface of the liver remains smooth, eventually combined with hypertrophy of other organs but not the spleen; chronic hypoglycaemia in the fasting condition combined with ketosis, after injection of adrenalin absence of or only a slight rise of blood sugar, but increased ketosis; abnormal blood sugar curve after giving different carbohydrates with or without any marked excretion of sugar in the urine.

On the other hand in hepatomegaly glycogenica a series of clinical and clinical-chemical symptoms which are present in other chronic liver affections (especially cirrhoses) are absent, e.g., jaundice, oedema, ascites, haemorrhages, enlargement of the spleen, glycosuria after giving galactose or fructose or both; further, a very marked increase of the globulin content of the blood serum and a strongly positive Takata-Ara reaction, and often a marked decrease of the amount of cholesterol esters in the serum\textsuperscript{34, 35}. Certain other symptoms of our patients certainly cannot be regarded as being typical of the glycogen liver; some other symptoms may or may not be. Urobilinuria was constantly absent in the case of the boy but not in that of the girl. The physical infantilism which both our children show is certainly not a typical symptom, neither is the familial character of the disease found by some investigators\textsuperscript{36}. A hepatic infantilism may occur in different parenchymatous liver affections as was recently clearly shown by Unshelm\textsuperscript{37}. It is important to note, however, that within a rather short time marked increase of growth took place in both our patients. Whether determination of blood glycogen, having regard to the number of leucocytes has any important significance in the differential diagnosis of chronic liver affection in childhood, cannot as yet be told. We are of the opinion, however, that in any case this may very probably hold true for investigating the possibility of splitting of glycogen as was described above.

From the series of cases of hepatomegaly glycogenica which were described recently it was probable, in view of the well-known dissociation of disturbances in liver function, that the intensity of some symptoms and the abnormalities in metabolism may vary, even in the same patient, e.g., the rise of blood sugar after giving carbohydrate and the degree of acetonuria. In both our patients there are also differences. Pathologically too the picture is not always the same; this is true for instance of the amount of
fat or connective tissue found in the liver which is accumulated with glycogen. In our boy the appearance of the liver as found at laparotomy and his general adiposity indicate that his liver contains much fat, just as in the first case of von Gierke. In the girl the constant urobilinuria and the weak positive Takata-Ara reaction (see above) indicate perhaps, that in her case the connective tissue is more increased (early cirrhosis?), as was found in the second case of von Gierke.

The morbid picture called 'stéatose hépatique massive' by Debré38, 39, which is also characterized by a very marked hypertrophy of the liver, beginning at a very early age, and in which biopsy indicates only the existence of a very large accumulation of fat in the liver, may show clinically not only an important difference from, but also a marked resemblance to, the picture of the glycogen liver. It has been described by different authors and was observed as a familial affection by Björn40 who also gives the results of the autopsy. In this affection glycosuria and hæmorrhages or sudden temporary changes in the size of the liver occur not infrequently. Results of investigations in the metabolism in cases of such enormous fat accumulations in the liver indicate without doubt that the differential diagnosis of hepatomegalia glycogenica and cases of 'stéatose hépatique massive' may be possible clinically, as by a thorough examination of the carbohydrate metabolism.

On several occasions one had an opportunity of confirming and extending the fundamental facts of glycogen disease, found post mortem by von Gierke and Schönheimer. It appeared that glycogen accumulation could give rise to marked hypertrophy also of other organs than liver and kidneys, heart (see Pompe41 and also Putschar42), pyloric muscle (personal communication, Deelman). We were able to investigate different organs of a baby with idiopathic hypertrophy of the heart, caused by accumulation of glycogen as first described by Pompe. In this case the adrenals were of normal size. We determined the glycogen content of the organs and studied the behaviour of the glycogen in some organs. We compared the results with those in the organs of a baby with very marked hypertrophy of both ventricles in a case of patent ventricular septum. Where the organs were not investigated immediately they were kept frozen. The glycogen content was determined in small pieces of the organs after hydrolysing with HCl (determinations of the glucose after the method of Hagedorn and Jensen). The following results were obtained (percentage figures):—Idiopathic hypertrophy of heart: heart, 7·96; liver, 9·18; spleen, 1·46; muscle, 9·39; lung, 0·084; spinal marrow, 0·588; adrenal, 1·25; blood, 18 mgm. (after death); hypertrophy of heart in patent intravent. septum: heart, 0·055 (L.V.), 0·07 (R.V.); liver, 0·103; kidney, 0·062; spleen, 0·01; muscle, 0·011; blood, 12·75 mgm. (during life). It must be remembered that both infants had passed through a period of fever shortly before death and that the autopsy was performed at least 24 hours after death, therefore, the determinations were done under circumstances in which there would normally be only traces of glycogen in the organs*.

* Our special thanks are due to Prof. de Vries, and to Dr. Hammer, for their kindness in giving us pieces of different organs.
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For comparison we give the results of glycogen determinations in some organs obtained by others in cases of glycogen diseases. Schönhheimer\(^a\):

Liver 10.48 per cent. glycogen in the fresh organ (38.72 per cent. of the dry substance).
Kidney 6.53 \(\ldots\) (36.82 \(\ldots\)).

Unshelm\(^b\):

Liver 14.2 \(\ldots\) (47.68 \(\ldots\)).

From our results one sees clearly the enormous increase of glycogen content, not only of the hypertrophic heart, but also of other organs, especially liver and muscle in this case of idiopathic hypertrophy of the heart. In the patient with septum defect in which the hypertrophy of the heart muscle was at least as marked as in the glycogen heart only very small amounts of glycogen were found in the available corresponding organs.

The results obtained in the glycogen heart correspond to those obtained by others in cases in which the hypertrophy concerned liver and kidneys. (Unshelm also found much glycogen in muscles and brain.)

The great stability of the glycogen in glycogen disease was first demonstrated by Schönhheimer in autolysis tests. The glycogen isolated from the organs (liver and kidneys) could, however, be split by fermentation; by addition of ground-up liver the glycogen was broken down within a short time. Unshelm demonstrated the same by mixing the ground-up liver of the patient with glycogen disease with ground liver of an adult.

In the glycogen heart we also investigated the stability and possibility of splitting of the glycogen. We investigated the decrease in the amount of glycogen in small pieces of heart muscle, on one hand, after keeping them for 48 hours at 37\(^o\) C.; on the other, after mixing with the same amount of heart muscle from a patient who died from meningitis, which latter tissue contained only traces of glycogen.

Glycogen heart alone: decrease from 7.86 to 6.74 per cent.

In mixing experiment: \(\ldots\), 7.86 \(\ldots\), 1.7 \(\ldots\).

Even under these conditions so extraordinarily favourable for glycogenolysis, the glycogen in the glycogen heart showed a notable stability which disappeared for the most part in mixing with heart muscle obtained from the meningitis patient.

Summary.

The results of new investigations performed in a boy with hepatomegaly and a particular disturbance in carbohydrate metabolism, formerly regarded as being the expression of an accumulation, especially in the liver, of glycogen which could only be mobilized with difficulty, are described. The investigations in a second case (a girl) with hepatomegaly and the same deviation in metabolism are also reported. The clinical history of this girl is given in detail.

The glycogen metabolism was especially studied in both patients. A method is given of determining the glycogen in 1 c.c. of blood. The question of the cause of the difficulty in splitting glycogen in glycogen disease in general was studied and is discussed. Some new facts of hepatomegaly
glycogenica were established and their value for the differential diagnosis from liver cirrhoses in childhood is stressed.

The distribution of glycogen in different organs and the stability of this glycogen in the heart was investigated in a case of cardiomegaly glycogenica and in a case of hypertrophy of the heart due to a patent septum ventriculorum.

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43. Creveld, S. v., see 18, 14.
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S. van Creveld

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